*Surg. Res. Comm.*, 1994, Vol. 16, pp. 219–237
Reprints available directly from the publisher
Photocopying permitted by license only

18



CL-294

# REVIEW PAPER: MOTILITY FACTORS IN CANCER INVASION AND METASTASIS

W.G. JIANG, M.B. HALLETT, and M.C.A. PUNTIS

*University Department of Surgery, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN*

*(Accepted for publication 13 February 1994)*

The motility of cancer cells is a crucial requirement for cancer invasion and metastasis. In the last decade, a number of factors, from a variety of sources, have been demonstrated to promote cancer cell motility. Here, we review the properties of these factors and discuss the mechanisms and signal transduction pathways involved. The implication for cancer treatment in the future is also discussed.

KEY WORDS: Motility factor, invasion, metastasis, hepatocyte growth factor, signal transduction

Abbreviations: **AMF**: autocrine motility factor; **CSF**: colony-stimulating factor; **EDMF**: Endothelioma derived motility factor; **GMF**: Glioma derived motility factor; **IFN**: interferon; **IIF**: invasion inhibitory factor; **IL**: interleukin; **IP**: insulin like peptides; **GF**: growth factor; **ISF**: invasion stimulating factor; **MDSF**: monocyte derived scattering factor; **MRP-1**: motility related protein-1; **MSF**: motility stimulating factor; **TNF**: tumour necrosis factor

## INTRODUCTION

Cancer metastasis is a complex phenomenon[1–3], involving primary proliferation of cells, their attachment to and invasion through the basement membrane and extracellular matrix, appearance in the circulation, re-attachment and migration through the endothelial layer, and finally the production of distant secondary tumours. The motility of cancer cells is thus a crucial step in the establishment of metastasis[4,5]. From the initial invasion through the basement membrane to the metastasis formation, cell motility is a basic requirement. It is thus important to establish the nature of the stimuli for increased cancer cell motility, the receptors utilised and the signal transduction mechanisms involved in inducing the cytoskeletal and cell adhesion molecule changes required for locomotion. This review will discuss the cytokine and other, more recently discovered, cancer cell motility factors, and their signal transduction pathways. Finally the possible implications for cancer treatment will be discussed.

## MOTILITY FACTORS

Motility factors (MFs) are factors which stimulate cell movement. It was reported early in the last decade that some cytokines can promote motility and invasion of cancer cells, and in the past few years more cytokines have been added to the list.

Table 1 Motility factors. The table summarises the known motility factors, their sources, and responding cell types.

| Motility Factor | Sources. | Responding Cells | References |
|---|---|---|---|
| IL-1 | Monocytes etc | Breast Cancer | 7 |
| IL-6 | Monocyte | Breast Cancer | 7,8 |
| GM-CSF | Various cell | Melanoma | 9 |
| | | Endothelial cells | 10 |
| | | Lung Ca cell | 11 |
| M-CSF(CSF-1) | Macrophages | Receptor(+ve) cell | 12 |
| G-CSF | Immune cells | Endothelial cells | 10 |
| HGF/SF | Fibroblasts | Various cell types | 13,14,15, |
| AMFs | Melanoma | Melanoma and malignant cells | 16,17 |
| | Prostatic Ca | Autocrine | 18,19,20 |
| | Fibrosarcoma | Autocrine | 21 |
| Autotaxin | Melanoma | Melanoma | 22 |
| MSF | Fibrosarcoma | Autocrine | 23,24 |
| IFN$_\gamma$ | Immune cells | Keratinocyte | 25 |
| FGF | Various cells | Brain tumours | 26 |
| | | Prostate Cancer | 27 |
| PDGF | Various cells | Brain tumours | 26 |
| | | Hematopoietic cells | 28 |
| IPs(IGF,insul) | Various cells | Melanoma, breast, and bladder Cancer | 17,29 |
| MDSF | Monocyte/mac | Human colon Cancer | 30 |
| TNFα | Monocyte | Various epithelial cells | 31 |
| EGF | Various cells | Brain tumours | 26 |
| | | Keratinocyte | 32 |
| TGFß | Various cells | Lung cancer | 33 |
| | | Keratinocyte | 32 |
| GMF | Glioma | Lung Cancer | 35,36 |
| MRP-1 | Various tumour | Breast Cancer | 37 |
| NGF | Nerve Tissue | Brain malignant tumour | 26 |
| Ca chemotactic Factor | Various Tumour | Hepatoma | 38 |
| EDMF | Endothelioma | Various tumour cells | 39 |
| ISF | ? | Prostatic Cancer | 40 |



In 1991, Stoker and Gheradi proposed a new term, motogen, to describe any factors which promote cell motility[6]. Generally, MFs can be categorised into three groups: factors stimulating motility only, factors stimulating both motility and growth, and a third group of other miscellaneous extracellular components and mediators. A comprehensive list of cancer cell motility factors thus includes a number of cytokines and other factors (Table 1).

Those factors which are solely motility factors are motility stimulating factor (MSF), autotaxin, glioma derived motility factor (GMF), cancer chemotactic factor, monocyte derived scattering factor (MDSF), and the endothelioma derived motility factor (EDMF), whereas other cytokine motility factors generally affect both motility and growth (Table 1).

One of the most powerful motility factors discovered to date is scatter factor, initially purified from fibroblasts[14,15] and found to be identical to hepatocyte growth factor[13,41,42]. This factor is both a potent motility factor for a variety of normal and malignant cells and also a growth regulator[6,13,14,15,30,43].

The MFs which affect both motility and growth may function in the following three ways. Some factors are stimulatory for both motility and growth, GM-CSF, IL-1, IGFs, PDGFs[26,28,29,44,45], while others are stimulatory for motility but inhibitory for growth (TGFß for example). Others motility factors can be either stimulatory or inhibitory for growth depending on the nature of target cells (for example TNF, inhibition for some colon, hepatic, and fibrosarcoma cells and stimulation for some of the gynecological tumour cells[46,47,48]). This suggests that regulation of motility and growth may occur via different pathways. Motility factors may also induce angiogenesis[49–53].

Cancer cell motility may also be promoted by some of the extracellular matrix (ECM) components, for example fibronectin[54,55], collagen IV[56,57], thrombospondin[58], and hyaluronan[59]. The ECM may therefore also provide a motility stimulation in cancer metastasis. The proteolytic enzyme, urokinase type plasminogen activator, also stimulates cell motility and invasion via a paracrine mechanism[60]. Other components may also promote cell locomotion, a cell surface glyco-conjugate has been reported to be important in controlling tumour cell motility[61] for example. Kojima et al[62] showed that tumour cells expressing ganglioside $G_{m3}$ on their surface greatly increase their spreading and motility by interacting with solid phase glycosphingolipids (Gg3). This indicates the important role of the carbohydrates on cell surface components in controlling cell motility.

The stroma and ECM are the environment in which tumour cells exist, and apart from offering growth factors which support cancer cell growth, and producing lytic enzymes (stromelysins)[65] which degrade the ECM allowing for easier cell migration, stromal cells of the tumour connective tissue (fibroblasts) are also a rich source of motility factors such as IL-6 and scatter factor. Immune cells, although they may play an important part in killing tumour cells, are also major contributors of motility factors such as IL-1, IL-6, TNFα, MDSF, HGF. T cells and monocyte/macrophages in particular provide a rich array of motility factors (Figure 1). The contribution of MFs from stroma, ECM, and immune cells has raised significant interest in re-assessing the role they play (particularly the immune cells) in tumour invasion and metastasis.

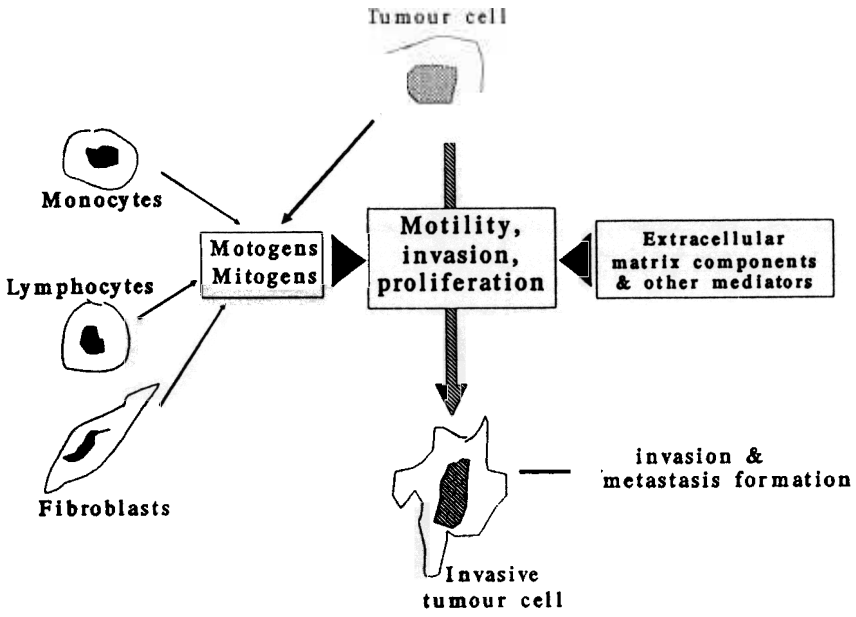


**Figure 1** The role of stromal fibroblasts, immune cells, and extracellular matrix in tumour cell motility and invasion.

*Autocrine and paracrine stimulation of motility*

Cell motility is affected by motility factors in two ways, autocrine and paracrine. The best examples for autocrine regulation are autocrine motility factor (AMF) and glioma motility factor (GMF), which are produced by malignant cells and stimulate motility in an autocrine manner. AMF, which is produced by melanoma cells and provide a potential autocrine stimulus for the cell[16,17], is actually a group of proteins which have both autocrine and paracrine stimulatory effects on cancer cells. Although initially the factor was shown to stimulate only motility, it has been shown very recently that AMF can also stimulates cell growth[19]. Some MFs have only paracrine activity, for example interferon gamma is produce by T lymphocytes but stimulates malignant cell motility. However, most factors have both autocrine and paracrine activity for cell motility, for example HGF/SF[14,15,42,30,43], IL-1 and IL-6[7]. The cross reaction between motility factors is less well studied. Although, experimentally, motility factors act individually, the effects of motility factors such as IL-1 and IL-6 may be additive[7].

## MECHANISMS AND INTRACELLULAR SIGNAL TRANSDUCTION IN CELL MOTILITY

Cell motility is an important area in both oncology and immunology, yet the precise mechanisms have not been clearly defined. There are however, some fundamental



differences between the motility of immune cells, such as neutrophils and cancer cells. In the former case, movement is directional, cells moving towards the source of a chemotactic factor along a concentration gradient. In contrast, motility factors cause cancer cells to increase motility in random directions. For example, experimentally, a tightly growing cell colony will be "scattered" by increased cell motility, giving rise to the name scatter factor. The speed of movement is also vastly different, neutrophil chemotaxis being observable under the microscope within minutes, whereas colony scattering takes hours. Despite these differences, the underlying processes are probably similar. Stimulation of cancer cell motility will involve stimulation, intracellular signalling, modifications of the interactions between the cytoskeleton and both the intracellular and extracellular environments (Figure 2). The following summarises the molecules and pathways which are involved in motility signal transduction.

*Protein kinase C(PKC)*: Protein kinase C is an important component in cell activation, including tumour cell transformation. It is also a key factor in mediating tumour cell motility and tumour invasion. Activation of PKC is associated with increased tumour cell motility/invasiveness and depletion of PKC may abolish motility/invasiveness of some cancer cells[66–69]. Although PKC may mediate motility in most tumour cells, activation of PKC in keratinocytes however may inhibit motility as reported recently by Ando et al[70], indicating that the down-stream pathways after activation of PKC may be different in different cell types.

*Protein kinase A(PKA)*: It has been suggested that protein kinase A is involved in the signal transduction pathway for GM-CSF-induced motility and metastasis of cancer cells[11]. This group has reported that inhibitors of PKA activity block the motility effect of GM-CSF and that cells with a defect in PKA fail to show increased motility and metastasis in response to GM-CSF.

*Tyrosine kinase*: Some of the motility factor receptors, in common with some growth factor receptors, have protein tyrosine kinase domains, raising the possibility that their signal transduction occurs via tyrosine phosphorylation. The best example for this signalling pathway is perhaps that with HGF/SF. The HGF receptor is the *c-met* proto-oncogene encoded protein[71,72] which is a transmembrane protein with 50 kDA alpha and 145 kDa beta subunits generated by cleavage of a single precursor[73,74,75]. The ß unit of the protein has both extra- and intra-celluar domains, the intracellular domain having a tyrosine kinase domain inducing tyrosine kinase activation[76]. A role in stimulating cell growth can be suggested perhaps involving activation of raf-1, MAPKK (mitogen activated protein kinase kinase), MAPK, and then *C-fos* and *c-jun* protooncogene and finally the nucleus transcription[77]. However, it is not clear whether tyrosine phosphorylation also plays a role in triggering increased cell motility, HGF/SF having effects on a number of important signalling molecules such as PLC gamma, GAP(GTPase activation protein), PI-3 kinase, and a soluble tyrosine kinase, src[78]. Mueller et al[79] have suggested a key role for tyrosine phosphorylation of a membrane protein, which may mediate tumour cell invasion via the cytoskeletal and plasma membrane events leading to the formation and function of "invadopodia".

*G protein coupling*: G proteins are small proteins which are involved in intracellular transduction. The G protein pathway consists of receptor, G protein, and effector. There is evidence that a small G protein *rho*-p21, which is related to *ras* p21 and

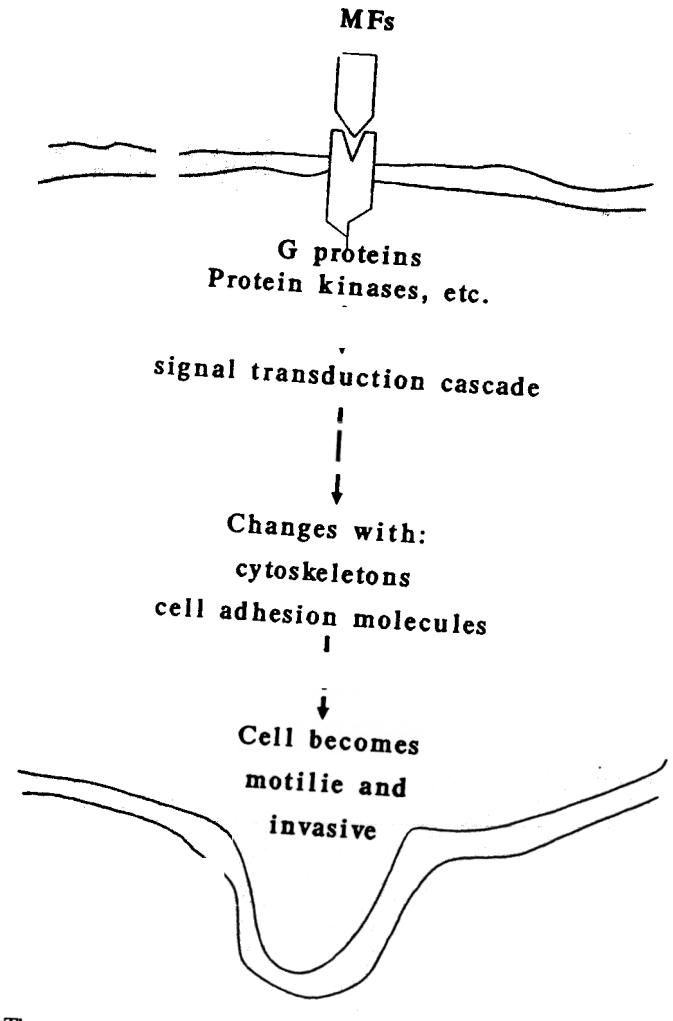


**Figure 2** The steps which motility factors (MFs) induce tumour cell motility and invasion.

reacting with *rho*-GDI, may regulate cell motility by acting on the actomyosin system[80]. In resting cells, *rho* p 21 is inactive and is present complexed to guanine diphosphate (GDP) and *rho* GDI (the inhibitory GDP/GTP exchange protein). These mask *rho*-p21 effector region. Upon stimulation (receptor ligand binding), the inhibitory action of *rho* GDI is released and the GDP-bound form of *rho* p21 becomes sensitive to the activation of *smg* GDS (the stimulatory GDP/GTP exchange protein) or *rho* GDS, *smg* GDS and *rho* GDS may therefore convert GDP to the GTP (guanine triphosphate)-bound active form. After this activation *rho* p21 opens its effector domain for interaction with other proteins, such as those involved in cell motility. AMF-stimulated cell motility occurs via a pertussis-sensitive G protein[19,21,81].



*Other intermediators*: Sadahira et al[83] recently reported that a specific endogenous molecule, sphingosine-1-phosphate is a unique signalling substance controlling cell motility and tumour cell invasiveness. It is the initial product of sphingosine degradation by sphingosine kinase and has specific effects on tumour cell motility without affecting protein kinase C, but perhaps by affecting organisational assembly of actin filament. Savarese et al[57], reported that cell motility stimulated by certain factors, for example, collagen IV may be mediated via an inositol 1,4,5-trisphosphate-independent release of $Ca^{2+}$ from intracellular stores but not via the pertussis toxin sensitive G protein. AMF stimulated cell motility, apart from the pertussis toxin sensitive G protein, may also involve binding to cell surface gp78[82,84] and may also involve inositol phosphate metabolite[17]. Cell surface expression of carbohydrate Gm3 may mediate cell motility by interacting with other cell surface or solid phase glycosphingolipids(GSLs). Motility and cell spreading occurs more rapidly, within 15 minutes, suggesting that GSL-GSL mediated early steps of the cell motility[62]. A cell surface glycoconjugate[61] had also been suggested to be a mediator of tumour cell invasion.

*Annexins*, are a group of calcium-dependent proteins associated with the cytoskeleton and in the case of annexin II, membrane. They bind to the cytoskeleton and to phopholipids and may be involved in mitotic signal transduction. They are found both in the cytoplasm and cell membrane[85], and may be associated with tumour cell adhesion and metastatic properties.

*Lipid mediators*: Lipoxygenase metabolites of arachidonic acid have effects on cell motility. 12(S)-HETE (hydroxyeicosatetraenoic acid) is stimulatory, whereas 13(S)-HODE (hydroxyoctadecadienoic acid) is inhibitory. Their regulation of tumour cell adhesion and spreading may occur via regulation of protein kinase C[86]. Chun et al[87] also confirm that lipoxygenase metabolites of arachidonic acid may serve as a second messenger in cell adhesion and spreading. Both lysophosphatidic acid (LPA) and phopholipase D (PLD)[88] have also been implicated in signalling motility.

*Cytoskeleton*: Rearrangement of the cytoskeleton is an important intracellular event in mediating cell motility. The receptor mediated signal must trigger changes in the cytoskeleton, usually with resultant changes in cell morphology for the generation of cell locomotion. Important cytoskeletal components of the cell motor includes F-actin, myosin, and possibly vimentin[90,91]. EGF induces changes in both actin and microtubule (tubulin) in tumour cells[91,92]. The pathway from receptor occupancy to cytoskeletal modification remains unclear, but lipid metabolites produced by lipoxygenase and cyclooxygenase[92] and $PIP_2$ have both been implicated in cytoskeletal actin regulation[101].

*Cell adhesion molecules*: Cadherins are major molecules in cell-cell connections. Loss of cadherin from tumour cells releases their attachment to each other and enables them to become motile and invasive. Tumours with high metastatic activity are reported to have impaired expression of cadherins[93,94,95,96,97]. Interestingly, HGF/SF can induce changes of E-cadherin in target cells[98,99].

*Effects of MFs on proteolytic enzymes*: Local degradation of ECM by proteases may also be an important step in the metastatic cascade[100,102,103]. ECM degradation may be regulated by the balance between metalloproteinase and plasminogen activator and their inhibitors[103]. This balance will be disturbed by a number of motogens. The

production of collagenase is increased by TNF-$\alpha$[104], IL-1[105,106,107] and bFGF[108,109]. Stromelysin is increased by IL-1, IL-6[105] and plasminogen activator is increased by IL-1[110], bFGF[111], laminin[112] and TNF-$\alpha$[113]. TIMP-2, a tissue inhibitor of metalloproteinase, can inhibit tumour cell invasion[114].

## THE POTENTIAL ROLE OF MOTILITY FACTORS IN MEDIATING CANCER CELL MOTILITY AND METASTASIS

The increased motility and invasion of tumour cells *in vivo* in response to motility factors may be due to the following changes: the increased levels of MFs in the body, the over expressed MF receptors, the defect in normal signal transduction, or a defect in negative control.

*Overproduction of motility factors*: Overproduction of motility factors, produced by either autocrine or paracrine mechanisms, will stimulate cancer cell motility. The changes of HGF/SF are well documented. Apart from liver damage, where it plays a role in liver regeneration, HGF levels increase in both blood and in other biological fluids in a number of conditions. After liver resection for metastatic tumours, HGF blood levels were increased[115]. Kaneko et al[116] showed that even higher levels of circulating HGF were produced by resection of metastatic foci in the liver. Routine surgical operations, such as cholecystectomy, colectomy and splenectomy induce significant increases of blood HGF[117]. Tumour cells, themselves, also produce HGF[15,63,118,119].

*Overexpression of motility factor receptors*: It has been shown that a variety of MF receptors are over-expressed in cancer cells. Expression of the HGF/SF receptor the *c-met* protein, in normal tissues, including gastro-intestinal mucosa, is either undetectable or there are low levels of mRNA for *cMET* (HGF receptor). However, expression is much higher in their related malignant counterparts, gastro-intestinal carcinoma, for example[120]. Over expression of this receptor is seen in various malignant tissues and in other transformed cells[121–127]. This raises the possibility that malignant cells expressing high levels of MF receptor will respond more sensitively or more vigorously to MF, and so become more motile than nonmalignant cells when exposed to MF.

*Unregulated activation of intracellular signalling for motility*: It has recently been discovered that cancer cells have a defective post-translational processing of *c-met* protein. Generation of the *c-met* protein involves the synthesis of 190kDa precursor protein and subsequent cleavage to form the alpha and beta subunits of the mature HGF receptor[76]. The activation of these mature receptors needs the binding of its ligand, HGF/SF. However, in some cancer cells, there is defective cleavage of the precursor protein, and the precursor 190kDa protein appears in the cancer cell membrane. This precursor is active without the ligand binding and the motility of cells bearing this receptor is increased and uncontrolled by HGF[128].

*Defect of negative control of cancer cell motility*: NM23 gene, encoding nucleoside diphosphate kinase (NDPK), has, in the past few years, been shown to be a metastasis suppressor gene. Transfection of NM23 genes greatly reduces tumour cell metastatic potential and paired DNA analysis shows that highly metastatic cell lines have a



deletion of one allele of NM23[129,130]. In cancer patients with colorectal cancer, breast Ca, malignant melanoma, hepatoma, and other tumours[130-134] a defect of this gene (and there may well be other metastatic suppressor genes) may relax the suppression of cancer cell motility and thus render them more susceptible to MFs.

## MOTILITY AS A TARGET IN CANCER TREATMENT

The recognition that cancer cell motility underlies metastasis, raises the possibility that strategies aimed at reducing motility will be effective anti-cancer therapies. The success of such an approach relies on identifying appropriate targets for such intervention.

*Motility inhibitory factors:*

Great efforts have been made to identify factors which may reduce cell motility/invasiveness and the followings are some of the successful ones.

*Invasion inhibiting factor-2 (IIF2)*: Isoai et al have purified two factors from liver which inhibit tumour invasion both *in vivo* and *in vitro*[135,136]. IIF-2 is particularly active when conjugated to albumin[136]. IIF-2 has amino acid sequence similarity to HMG 17 (High Mobility Group 17), a highly conserved nuclear protein which may regulate DNA structure and whose expression is down-regulated during differentiation[136,137,138].

*MRP-1* has been shown to inhibit motility of various cell types[37]. Sequence analysis of MRP-1 revealed similarities with CD37, ME491 (melanoma-associated antigen), TAPA-1 (antiproliferative antibody), CO-029 (a human tumour associated antigen), CD9, and sm23 antigen. This has raised interest in searching for roles in motility for these antigens. It has recently been reported that transfection of malignant cells with MRP-1 DNA results in a significant reduction in motility and metastasis[139].

*Cell motility inhibitory protein*, a protein isolated from Dunning cancer cells[140], also significantly inhibits cancer cell motility.

## ANTI-MOTILITY AGENTS

*Retinoids* are a group of vitamin A metabolites and synthetic analogues which interact with processes involved in growth and differentiation. They also suppress cell motility and invasion (*in vitro*) and metastasis (*in vivo*)[141,142,143,144,145]. Interestingly, retinoic acid reduces the expression of AMF receptor[122,143].

A highly conserved sequence from the matrix metalloproteinase enzyme prosegment has been shown to inhibit tumour cell invasion at a cellular level, indicating the importance of matrix in both tumour cell invasion and metastasis[147].

*The tripeptide Arg-Gly-Asp (RGD)*, the active component of fibronectin[148,149], is important in other cell adhesion proteins[150] which bind to the members of integrin family of the cell adhesion molecules. RGD containing peptides have been shown to inhibit tumour cell adhesion and tumour progression in experimental animals[148,151], and fibronectin stimulated tumour cell motility[152]. Chambers et al[153] showed that

metastatic cells express high level of osteopontin (OPN), a phosphoprotein containing RGD peptides, and this promotes cell spreading on and adhesion to OPN itself and also on laminin. This effect on spreading is blocked completely by the RGD sequence. A wide range of other RGD containing proteins and peptides have been tested and found to have anti-motility and metastasis activities[154,155]. Apart from RGD sequence containing peptides, other ECM components were also explored. Laminin peptide 11, has been shown to inhibit tumour motility and therefore invasion presumably by binding to the laminin receptor[156].

*Antibodies* against a cell surface glycoconjugate have been shown to inhibit tumour cell motility and tumour metastasis indicating the usefulness of anti-motility agents in cancer treatment[61]. Anti-specific glycosphingolipid antibody also inhibits cell motility, spreading and adhesion[62]. Antibodies against integrin receptors on the cell surface have been shown to inhibit cell migration, invasion and tumour metastasis[157,158]. This area is a promising area and further progress is anticipated in the near future.

*Suramin*, a trypan red derivative was found to inhibit cell motility at a lower concentration than caused growth inhibition[27]. It also prevents melanoma cells spreading on ECM[159]. This agent has been used in patients with adrenocortical carcinoma and prostatic cancers[160,161]. The effect of suramin on cancer cells may be via inhibition of both motility and invasion, and also of growth.

*Anti-cytoskeleton structure agents* have also been explored. Microtubule associated protein inhibitor, estramustine phosphate has been shown to inhibit cell motility which provides another interesting area to investigate[162]. Taxol is a natural product of Western Yew and can deform the cytoskeleton. This agent has been used in patients with cancer but more work is needed to confirm the effects[146].

*Motility factor antagonist*: The use of functionally inactive antagonists of MFs has been explored. HGF antagonists have recently been reported, which compete with receptors for HGF binding but without inducing any biological effects[163,164]. Synthetic enzymatically inactive urokinase-type plasminogen activator, which may bind to the cell surface receptor for uPA, has been reported recently[165,166]. Saturation of uPA receptor with these non-active antagonists may greatly reduce tumour cell invasion and metastasis both *in vitro* and *in vivo*.

*Anti-motility signalling:* Calmodulin antagonists which inhibit calmodulin-dependent pathways inhibit motility and invasion[167]. The PKC inhibitors staurosporine, H-7, MDL 27,032[168,169], SPC100221 (or threo-dihydrosphingosine)[170] and PKC-inhibitory retinoids[171] all inhibit motility and invasion *in vitro* as well as metastasis *in vivo* in animal studies. G-protein cascade can be blocked by carboxyamid-amino-imidazol compound and this results in inhibition of tumour cell invasion and motility[167].

Recently, Kohn et al[172] has reported a novel inhibitor of selected signal transduction pathways, whereby CAI (L651582, NSC 609974) inhibits anchorage dependent and independent growth of a large series of human cancer cell lines, and also inhibits experimental metastases, presumably by inhibiting the signal transduction pathways (the release of arachidonic acid, and the generation of phosphoinositides). This provides evidence that inhibiting specific signal transduction routes may be an important approach in cancer treatment.

Since it has been shown that arachidonic acid lipoxygenase metabolites are second messengers for cell spreading[86,87], blocking the pathway of metabolism by various inhibitors may be another approach for treatment.



*Genetic approach*

Regulation of cell motility at genetic level is less well investigated. However, transfection, *in vitro* of the nm23 gene, which is defective is some metastatic and highly invasive tumours, has been shown to suppress tumour invasive and metastatic potential of a human tumour[173]. Extension of this approach *in vivo* would provide an interesting and powerful approach to reducing cancer metastasis. Antisense RNA to *c-myc* has also been shown to inhibit cell motility[174].

## SUMMARY AND FUTURE WORKS:

Motility factors play a very important part in cancer metastasis. As more motility factors are identified, we will be able to develop a more thorough understanding of the invasive nature of cancer cells. Although there are many unanswered questions, there is no doubt that strategies aimed at reducing tumour cell motility and invasion should be designed and investigated.

*Acknowledgements*

We thank Scotia Pharmaceuticals Ltd and Arthritis and Rheumatism Research Council (UK) for supporting this work.

*References*

1. Liotta L.A. (1987) Biochemical mechanisms of tumor invasion and metastases. *Clin Physiol Biochem*, **5**, 190–199.
2. Liotta LA; Stracke M.L. (1988) Tumor invasion and metastases: biochemical mechanisms. *Cancer Treat Res*, **40**, 223–238.
3. Miller F.R. Immune mechanisms in the sequential steps of metastasis. *Crit Rev Oncogenesis*, **4**, 293–311.
4. Schiffmann E. (1990) Motility as a principal requirement for metastasis. *Cancer Invest.*, **8**, 673–674.
5. Liotta L.A., Rao C.N., Wewer U.M. (1986) Biochemical interactions of tumor cells with the basement membrane. *Ann Rev Biochem*, **55**, 1037–1057.
6. Stoker M. and Gherardi E. (1991) Regulation of cell movement. *Biochim Biophys Acta.*, **1072**, 81–102.
7. Verhasselt B., Van Damme J., van Lareveke N., Put W., Bracke M., De Potter C. and Mareel M. (1992). Interleukin-1 is a motility factor for human breast carcinoma cells in vitro: additive effect with Interleukin-6. *Eur J Cell Biol.*, **59**, 449–457.
8. Tamm I., Cardinale I., Krueger J., Murphy J.S., May L.T., and Sehgal P.B. (1989). Interleukin-6 decreases cell-cell association and increases motility of ductal breast carcinoma cells. *J Exp Med*, **170**, 1649–1669.
9. Kohn E.C., Hollister G.H., Dipersio J.D., Wahl S., Liotta L.A. and Schiffmann E. (1993) Granulocyte-macrophage colony-stimulating factor induces human melanoma cell migration. *Int J Cancer.* **53**, 968–972.
10. Bussolino F., Wang J.M., Defilippi P., Turrini F., Sanavio F., Edgell C.J.S., Aglietta M., Arese P., and Mantovani A. (1989) Granulocyte- and granulocyte-macrophage-colony stimulating factor induce human endothelial cells to migrate and proliferate. *Nature*, **337**, 471–473.

11. Young M.R., Lozano Y., Djordjevic A., Devata S., Matthews J., Young M.E., Wright M.A. (1993) Granulocyte-macrophage colony-stimulating factor stimulates the metastatic properties of Lewis lung carcinoma cells through a protein kinase A signal-transduction pathway. *Int J Cancer*, **53**. 667–671.
12. Filderman A.E., Bruckner A., Kacinski B.M., Deng N., and Gemold H.G. (1992) Macrophage-colony-stimulating factor (CSF-1) enhances invasiveness in CSF-1 receptor-positive carcinoma cell lines. *Cancer Res*, **52**, 3661–3666.
13. Weidner K.M., Arakaki N., Hartmann G., Vandekerckhove J., Weingart S., Rieder H., Fonatsch C., Tsubouchi H., Hishida T., Daikuhara Y., and Birchmeier W. (1991) Evidence for the identity of human scatter factor and human hepatocyte growth factor. *Proc Natl Acad Sci USA*. **88**, 7001–7005.
14. Stoker M., Perryman M. (1985) An epithelial scatter factor released by embryo fibroblasts. *J Cell Sci*, **77**, 209–223.
15. Stoker M., Gheradi E., Perryman M., and Gray J. (1987) Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. *Nature*, **327**, 239–242.
16. Liotta L.A., Mandler R., Murano G., Katz D.A., Gordon R.K., Chiang P.K., and Schiffmann E.S. (1986) Tumor cell autocrine motility factor. *Proc Natl Acad Sci USA*, **83**, 3302–3306.
17. Kohn E.C., Liotta L.A., and Schiffmann E. (1990). Autocrine motility factor stimulates a three-fold increase in inositol trisphosphate in human melanoma cells. *Biochem Biophys Res, Commun.*, **166**, 757–764.
18. Evans C.P., Walsh D.S., and Kohn E. (1991) An autocrine motility factor secreted by the Dunning R-3327 rat prostatic adenocarcinoma cell subtype AT21. *Int J Cancer*, **49**, 109–113.
19. Silletti S., Watanabe H., Hogan V., Nabi I.R., Raz A. (1991) Purification of B16-F1 melanoma autocrine motility factor and its receptor. *Cancer Res*, **51**, 3507–3511.
20. Watanabe H., Nabi I.R., Raz A. (1991) The relationship between motility factor receptor internalization and the lung colonization capacity of murine melanoma cells. *Cancer Res*, **51**, 2699–2705.
21. Watanabe H., Carmi P., Hogan V., Raz T., Silletti S., Nabi I.R., and Raz A. (1991) Purification of human tumor cell autocrine motility factor and molecular cloning of its receptor. *J Biol Chem*, **266**, 13442–13448.
22. Stracke M.L., Krutzsch H.C., Unsworth E.J., Arestad A., Coice V., Schiffmann E., and Liotta L.A. (1992) Identification, purification, and partial sequence analysis of autotaxin, a novel motility-stimulating protein. *J Biol Chem*, **267**, 2524–2529.
23. Grey A.M., Schor A.M., Rushton G., Ellis I., Schor S.L. (1989) Purification of the migration stimulating factor produced by fetal and breast cancer patients fibroblasts. *Proc Natl Acad Sci USA*, **86**, 2438–2442.
24. Schor S.L., Schor A.M., Grey A.M., Rushton G. (1988) Foetal and cancer patient fibroblasts produce an autocrine migration-stimulating factor not made by normal adult cells. *J Cell Sci*, **90**, 391–399.
25. Nickoloff B.J., Mitra R.S., Riser B.L., Dixit V.M., Varani J. (1988) Modulation of keratinocyte motility. Correlation with production of extra cellular matrix molecules in response to growth promoting and antiproliferative factors. *Am J Pathol*, **132**, 543–551.
26. Engebraaten O., Bjerkvig R., Pedersen P.H., and Laerum O.D. (1993) The effects of EGF, bFGF, NGF, and PDGF(BB) on cell proleferative, migratory and invasive capacities of human brain-tumor biopsies *in vitro*. *Int J Cancer*, **53**, 209–214.
27. Pienta K.J., Isaacs W.B., Vindivich D., and Coffey S. (1991) The effects of basic fibroblast growth factor and suramin on cell motility and growth of rat prostate cancer cells. *J Urol.* **145**, 199–202.
28. Matsui T., Pierce J.H., Fleming T.P., Greenberger J.S., LaRochelle W.J., Ruggiero M. and Aaronson S.A. (1989) Independent expression of human alpha or beta platelet-derived growth factor receptor cDNAs is a naive hematopoietic cell leads to functional coupling with mitogenic and chemotactic signalling pathways. *Proc Natl Acad Sci USA*, **86**, 8314–8318.
29. Kohn E.C., Francis E.A., Liotta L.A., and Schiffmann E. (1990) Heterogeneity of the motility responses in malignant tumor cells: a biological basis for the diversity and homing of metastatic cells. *Int J Cancer*, **46**, 287–292.
30. Jiang W.G., Hallett M.B., and Puntis M.C.A. (1993) Monocyte conditioned medium possess a novel factor which increase motility of cancer cells. *Int J Cancer*, **53**, 426–431.
31. Rosen E.M., Goldberg I.D., Liu D., Setter E., Donovan M.A., Bhargava M., Reisss M., and Kacinski B.M. (1991) Tumor necrosis factor stimulates epithelial tumor cell motility. *Cancer Res*, **51**, 5313–5321.
32. Barrandon Y. and Green H. (1987) Cell migration is essential for sustained growth of keratinocyte colonies: the roles of transforming growth factor-a and epidermal growth factor. *Cell*, **50**, 1131–1137.





33. Mooradian D.L., McCarthy J.B., Komanduri K.V., and Furcht L.T. (1992) Effects of transforming growth factor ß1 on human pulmonary adenocarcinoma cell adhesion, motility, and invasion *in vitro*. *J Nat Cancer Instit.*, **84**, 523–527.
34. Ohnishi T., Arita N., Hayakawa T., Kawahara K., Kato K. and Kakinuma (1993) Purification of motility factor from human malignant glioma cells and its biological significance in tumor invasion. *Biochem Biophys Res Commun*, **193**, 518–525.
35. Cuttitta F., Carney D.N., Mulshine J., Moody T.W., Fedorko J., Fischler A., Minna J.D. (1985) Bombesin-like peptides can function as autocrine growth factors in human small-cell lung cancer. *Nature*, **316**, 823–826.
36. Ruff, M., Schiffmann, E., Terranova, V., Pert, C.B. (1985) Neuropeptides are chemoattractants for human tumor cells and monocytes: a possible mechanism for metastasis. *Clin Immunol Immunopathol*, **37**, 387–396.
37. Miyake M., Koyama M., Seno M., and Ikeyama. (1991) Identification of the motility-related protein (MRP-1), recognized by monoclonal antibody M31-15, which inhibits cell motility. *J Exp Med*, **174**, 1347–1354.
38. Yoshida K., Ozaki T, Ushijina K, Hayashi H. (1970) Studies on the mechanisms of invasion in cancer. I. Isolation and purification of a factor chemotactic for cancer cells. *Int J Cancer*, **6**, 123–132.
39. Taraboletti G., Belotti D., Dejana E., Mantovani A., and Giavazzi R. (1993) Endothelial cell migration and invasiveness are induced by a soluble factor produced by murine endothelioma cells transformed by polyoma virus middle T oncogene. *Cancer Res*, **53**, 3812–3816.
40. Stearns M.E., and Stearns M. (1993) Autocrine factors, type IV collagenase secretion and prostatic cancer cell invasion. *Cancer Metastasis Rev.*, **12**, 39–52.
41. Nakamura T. Nishizawa T. Hagiya M. Seki T. Shimonishi M. Sugimura A. Tashiro K. Shimizu S. (1989) Molecular cloning and expression of human hepatocyte growth factor. *Nature*, **342**, 440–3.
42. Gherardi E., and Stoker M. (1990) Hepatocyte and scatter factor. *Nature*, **346**, 228.
43. Tajima H., Matsumoto K., Nakamura T. (1992) Regulation of cell growth and motility by hepatocyte growth factor and receptor expression in various cell species. *Exp Cell Res*, **202**, 423–431.
44. Foulke R.S., Marshall M.H., Trotta P.P., and von Hoff D.D. (1990) *In vitro* assessment of the effects of granulocyte-macrophage colony-stimulating factor on primary human tumors and derived lines. *Cancer Res*, **50**, 6264–6267.
45. Hamburger A.W., Lurie K.A., and Condon M.E. (1987) Stimulation of anchorage-independent growth of human tumor cells by interleukin-1. *Cancer Res*, **47**, 5612–5615.
46. Balkwill F. (1993) Tumour necrosis factor: improving on the formula. *Nature*, **361**, 206–207.
47. Qin Z., Kruger-Krasagakes S., Kunzendorf U., Hock H., Diamantstein T., and Blankenstein T. (1993) Expression of tumor necrosis factor by different tumor cell lines results either in tumor suppression or augmented metastasis. *J Exp Med*, **178**, 355–360.
48. Orosz P., Echtenacher B., Falk W., Ruschorff J., Weber D., and Mannel. (1993) Enhancement of experimental metastasis by tumor necrosis factor. *J Exp Med*, **177**, 1391–1398.
49. Blood C.H., Zetter B.R. (1990) Tumor interactions with the vasculature: angiogenesis and tumor metastasis. *Biochim Biophys Acta*, **1032**, 89–118.
50. Comoglio P.M., Di Renzo M.F., Naldini L., Olivero M., Gaudino G., Tamagnone L., and Bussolino F. (1993) Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial-cell motility and growth. *J Cell Biochem*, **S17A**, 232.
51. Grant D.S., Kleinman H.K., Goldberg I.D., Bhargava M.M., Nickoloff B.J., Kinsella J.L. Polverini P., and Rosen E.M. (1993) Scatter factor induces blood-vessel formation in vivo. *Proc Natl Acad Sci USA*, **90**, 1937–1941.
52. Bussolino F., DiRenzo 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.
53. Kim K.J., Li B., Winter J., Armanini M., Gillett N., Phillips H.S., and Ferrara N. (1993) Inhibition of vascular endothelial growth factor induced angiogenesis suppresses tumour growth in vivo. *Nature*, **362**, 841–846.
54. Lacovera J., Cramer E.B., and Quigley J.P. (1984) Fibronectin enhancement of directed migration of B 16 melanoma cells. *Cancer Res*, **44**, 1655–1663.
55. McCarthy J.B., Hagen S.T., and Furcht L.T. (1986) Human fibronectin contains distinct adhesion- and motility-promoting domains for metastatic melanoma cells. *J Cell Biol*, **102**, 179–188.

56. Chelberg M.K., Tsilibary E.C., Hauser A.R., and McCarthy J.P. (1989) Type IV collagen-mediated melanoma cell adhesion and migration: involvement of multiple, distinct domains of the collagen molecule. *Cancer Res*, **49**, 4797–4802.
57. Savarese D.M.F., Russell J.T., Fatatis A., and Liotta L.A. (1992) Type IV collagen stimulates an increase in intracellular calcium. Potential role in tumor cell motility. *J Biol Chem*, **267**, 21928–21935.
58. Yabkowitz R., Mansfield P.J., Dixit V.M., and Suchard S.J. (1993) Motility of human carcinoma cells in response to thrombospondin: relationship to metastatic potential and thrombospondin structural domains. *Cancer Res*, **53**, 378–387.
59. Turley E.A. (1992) Hyaluronan and cell locomotion. *Cancer Metastasis Rev*, **11**, 21–30.
60. Ossowski L., Clunie G., Masucci M.T., and Blasi F. (1991) *In vitro* paracrine interation between urokinase and its receptor: effect on tumor cell invasion. *J Cell Biol*, **115**, 1107–1112.
61. Miyake M. and Hakomori S. (1991) A specific cell surface glycoconjugate controlling cell motility: evidence by functional monoclonal antibodies that inhibits cell motility and tumour cells metastasis. *Biochem*, **30**, 3328–3334.
62. Kojima N. and Hakomori S. (1991) Cell adhesion, spreading, and motility of $G_{m3}$-expression cells based on glycolipid-glycolipid interaction. *J Biol Chem*, **266**, 17552–17588.
63. Tsao M.S., Shu H., Giaid A., Viallet J., and Park M. (1993) Hepatocyte growth-factor/scatter factor (HGF/SF) is an autocrine factor expressed by human normal bronchial epithelial (NSB) and nonsmall cell lung-carcinoma (NSCLC) cells. *FASEB J*, **7**, 429.
64. Tsao M.S., Zhu H., Giaid A., Wiallet J., Nakamura T. and Park M. (1993) Hepatocyte growth factor/scatter factor is an autocine factor for human normal bronchial epithelial and lung carcinoma cells. *Cell Growth Differet*, **4**, 571–579.
65. Van den Hooff A. (1991) The role of stromal cells in tumor metastasis: a new link. *Cancer Cell*, **3**, 186–187.
66. Feuerstein N. and Cooper H.L. (1984) TI studies of the differentialtion of promyelocyte cells by phobol ester I induction of discrete membrane proteins characteristic of monocytes and expression of motility functions in HL-60 cells following differentiation oby phorbol ester. *Biochim Biophys Acta*, **781**, 239–246.
67. Gopalakrishna R., Barsky S.H. (1988) Tumor promoter-induced membrane-bound protein kinase C regulates hematogenous metastasis. *Proc Natl Acad Sci USA*, **85**, 612–616.
68. Takenaga K., Takahashi K. (1990) Effects of 12-*O*-tetradecanoylphorbol-13-acetate on adhesiveness and lung-colonizing ability of Lewis lung carcinoma cells. *Cancer Res*, **46**, 375–380.
69. Isakov V., Gopas J., Priel E. (1991) Effect of protein kinase C activating tumor promoters on metastases formation by fibrosarcoma cells. *Invasion Metastasis*, **11**, 14–24.
70. Ando Y., Lazarus G.S. and Jensen P. (1993) Activation of protein kinase C inhibits human keratinocyte migration. *J Cell Physiol*, **156**, 487–496.
71. Bottaro D.P., Rubin J.S., Faletto D.L., Chan A.M.L., Kmiecik T.E., Vande Woude G.F., and Aaronson S.A. (1991) Identification of the hepatocyte growth factor as the c-MET protooncogene product. *Science*, **258**, 802–804.
72. Naldini L., Weidner K.M., Vigna E., Gaudino G., Bardelli A., Ponzetto C., Narsimhan R.P., Hartmann G., Zarnegar R., Michalopoulos G.K. et al. (1991) Scatter factor and hepatocyte growth factor are indistinguishable ligands for the MET receptor. *Embo J.*, **10**, 2867–78.
73. Park M., Dean M., Kaul K., Braun M.J., Gonda M.A., and Vande Woude G.F. (1987) Sequence of MET protooncogene cDNA has features characteristic of the tyrosine family of growth factor receptors. *Proc Natl Acad Sci USA*, **84**, 6379–6383.
74. Gonzatti-Haces M., Seth A., Park M., Gopeland T., Oroszlan S., and Vande Woude G.F. (1989) Characterization of the TPR-MET oncogene p65 and the MET protooncogene p140 protein tyrosine kinase. *Proc Natl Acad Sci USA*, **85**, 21–25.
75. Giordano S., DiRenzo M.F., Narsimhau R.P., Copper C.S. et al. (1989) Biosynthesis of the protein encoded by the *c-met* proto-oncogene. *Oncogene*, **4**, 1383–1388.
76. Cooper C.S. (1992) The *met* oncogene: from detection by transfection to transmembrane receptor for hepatocyte growth factor. *Oncogene*, **7**, 3–7.
77. Roberts T.M. (1992) A signal chain of events. *Nature*, **360**, 534–535.
78. Faletto D.L., Kaplan D.R., Halverson D.O., Rosen E.M., and Vande Wounde G.F. (1992) Signal transduction of in c-met mediated motogenesis. In *Hepatocyte growth factor-scatter factor (HGF/SF) and the c-met receptor* edited by Goldberg I.D., Birkhauser Verlag, Basel, pp. 107–130.





79. Mueller S.C., Yeh Y., and Chen W.T. (1992) Tyrosine phosphorylation of membrane proteins mediateds cellular invasion by transformed cells. *J Cell Biol*, **119**, 1309–1325.
80. Takaishi K., Kihuchi A., Kuroda S., Kotani K., Sasaki T. and Takai Y. (1993) Involvement of *rho* p21 and its inhibiotory GDP/GTP exchange protein (*rho* GDI) in cell motility. *Mol Cell Biol*, **13**, 72–79.
81. Watanabe H., Carmi P., Hogan V., Raz T., Silletti S., Nabi I.R., Raz A. (1991) Purification of human tumor cell autocrine motility factor and molecular cloning of its receptor. *J Bioll Chem.*, **266**, 13442–13448.
82. Silletti S. and Raz A. (1993) Autocine motility factor is a growth factor. *Biochem. Biophys Res Commun.*, **194**, 446–457.
83. Sadahira Y., Ruan F., Hakomori S., and Igarashi Y. (1993) Sphingosine 1-phosphate, a specific endogenous signalling molecule controlling cell motility and tumor cell invasiveness. *Proc Natl Acd Sci USA*, **89**, 9686–9690.
84. Nabi I.R., Watanabe H., Silletti S., Raz A. (1991) Tumor cell autocrine motility factor receptor. *Exs*, **59**, 163–177.
85. Yeatman T.J., Updyke T.V., Kaetzel M.A., Dedman J.R., Nicolson G.L. (1993) Expression of annexins on the surfaces of non-metastatic and metastatic human and rodent tumor cells. *Clin Exp Metastasis*, **11**, 37–44.
86. Liu B., Timar J., Howlett J., Diglio C.A., and Honn K.V. (1992) Lipoxygenase metabolites of arachidonic and linoleic acids modulate the adhesion of tumour cells to endothelium via regulation of protein kinase C. *Cell Regulation*, **2**, 1045–1055.
87. Chun J.S. and Jacobson B.S. (1992) Spreading of HeLa cells on a collagen substratum requires a second messenger formed by the lipoxygenase metabolm of arachidonic acid released by collagen receptor clustering. *Mol Biol Cell*, **3**, 481–492.
88. Imamura F., Horai T., Mukai M., Shinkai K., Sawada M., and Akedo H. (1993) Induction of *in vitro* tumor cell invasion of cellular monolayers by lysophosphatidic acid or phospholipase D. *Biochem Biophys Res Commun.*, **193**, 497–503.
89. Dowrick P.G., and Warn R.M. (1990) The effects of scatter factor on the cytoskeletal organization of epithelial cells. *Cancer Invest.*, **8**, 675–683.
90. Rosen E.M., Meromsky L., Goldberg I., Bhargava M., Setter E. (1990) Studies on the mechanism of scatter factor. Effects of agents that modulate intracellular signal transduction, macromolecule synthesis and cytoskeleton assembly. *J Cell Sci*, **96**, 639–649.
91. Lichtner R.B., Wiedemuth M., Noeske-Jungblut C., Schirrmacher V. (1993) Rapid effects of EGF on cytoskeletal structures and adhesive properties of highly metastatic rat mammary adenocarcinoma cells. *Clin Exp Metastasis*, **11**, 113–125.
92. Peppelenbosch M.P., Tertoolen L.G.J., Hage W.J., and de Laat S.W. (1993) Epidermal growth factor induced actin remodeling is regulated by 5-lipoxygenase and cyclooxygenase products. *Cell*, **74**, 565–575.
93. Doki Y., Shiozaki H., Tahara H., Inoue M., Oda H., Iihara K., Kadowaki T., Takeichi M., and Mori T. (1993) Correlation between E-cadherin expression and invasiveness *in vitro* in a human esophageal cancer cell line. *Cancer Res*, **53**, 3421–3426.
94. Shiozaki H., Tahara H., Oka H., Miyata M., Kobayashi K., Tamura S., Iihara K., Doki Y., Hirano S., Takeichi M. and Mori T. (1991) Expression of immunoreactive E-cadherin adhesion molecules in human cancers. *Am J Path*, **139**, 17–23.
95. Oka, Shiozaki H., Kobayashi K., Inoue M., Tahara H., Kobayashi T., Takatsuka Y., Matruyoshi N., Hirano S., Takeichi M., and Mori T. (1993) Expression of E-cadherin cell adhesion molecules in human breast cancer tissues and its relationship to metastasis. *Cancer Res*, **53**, 1696–1701.
96. Schipper J.H., Frixen U.H., Behrens J., Unger A., Jahnke D. and Birchmeier W. (1991) E-cadherin expression in squamous cell carcinomas of head and neck. *Cancer Res.*, **51**, 6328–6337.
97. Behrens J., Mareel M.M., Van R.F., and Birchmeier W. (1989) Dissecting tumor cell invasion. *J Cell Biol*, **108**, 2435–2447.
98. Behrens J., Weidner K.M., Frixen U.H., Schipper J.H., Sachs M., Arakaki N., Daikuhara Y. and Birchmeier. (1991) The role of E-cadherin and scatter factor in tumour invasion and cell motility. In *Cell motility factors* edited by Goldberg I.D., by Birkharser Verlag Basel, Switzerland.
99. Watane M., Matsumoto K., Nakamura T. and Takeichi M. (1993) Effect of hepatocyte growth factor on cadherin mediated cell-cell adhesion. *Cell Structure Function*, **18**, 117–124.
100. Duffy M.J. (1987) Do proteases play a role in cancer invasion and metastasis. *Eur J Cancer Clin Oncol.* **23**, 583–89.

1. Janmey P.A. and Stossel T.P. (1987) Modulation of gelsolin function by phosphatidylinositol 4,5-biphosphate. *Nature*, **325**, 362–364.
2. Mullins D.E., Rohrlick S.T. (1983) The role of proteinases in cellular invasiveness. *Biochim Biophys Acta.*, **695**, 177–214.
3. Mignatti P. and Rifkin D.B. (1993) Biology and biochemistry of proteinases in tumor invasion. *Physiol Rev.*, **73**, 161–194.
4. Okada Y., Tsuchiya H., Shimizu H., Tomita K., Nakanishi I., Sato H., Seiki M., Yamashita K., Hayakawa T. (1990) Induction and stimulation of 92-kDa gelatinase/type IV collagenase production in osteosarcoma and fibrosarcoma cell lines by tumor necrosis factor alpha. *Biochem Biophys Res Commun.*, **171**, 160.
5. Ito A., Sato T., Iga T., Mori Y. (1990) Tumor necrosis factor bifunctionally regulates matrix metalloproteinases and tissue inhibitor of metalloproteinasess (TIMP) production by human fibroblasts. *FEBS Lett*, **269**, 93.
6. Postlethwaite A.E., Lachman L.B., Mainardi C.L., Kang A.H. (1983) Interleukin 1 stimulation of collagenase production by cultured fibroblasts. *J Exp Med*, **157**, 801.
7. Sato T., Ito A., Mori Y. (1990) Interleukin-6 enhances the production of tissue inhibitor of metalloproteinases (TIMP) but not that of matrix metalloproteinases by human fibroblasts. *Biochem Biophys Res Commun.*, **170**, 824.
8. Brown P.D., Levy A.T., Margulies I.M.K., Liotta L.A., Setler-Stevenson W.G. (1990) Independent expression and cellular processing of Mr 72,000 type IV collagenase and interstitial collagenase in human tumourigenic cell lines. *Cancer Res.*, **50**, 6184.
9. Buckley-Sturrock A., Woodward S.C., Senior R.M., Griffin G.L., Klagsbrun M., Davidson J.M. (1989) Deferential stimulation of collagenase and chemotactic activity in fibroblasts derived from rat wound repair tissue and human skin by growth factors. *J Cell Phyiol*, **138**, 70.
10. Michel J.B., Quertermous T. (1989) Modulation of mRNA levels for urinary- and tissue-type plasminogen activator and plasminogen activator inhibitor 1 and 2 in human fibroblasts by interleukin-1. *J Immunol*, **143**, 890.
11. Presta M., Maiser J.A.M., Ragnotti G. (1989) The mitogenic signalling pathway but not the plasminogen activator-inducing pathway of basic fibroblast growth factor is mediated through protein kinase C in fetal bovine aortic endothelial cells. *J Cell Biol*, **109**, 1877.
12. Pourreau-Schneider N., Delori P., Boutiere B., Arnouz D., George F., Sampol J., Martin P.M. (1989) Modulation of plasminogen activator systems by matrix components in two breast cancer cell liness, MCF-7 and MDA-MB-231. *J Natl Cancer Inst*, **81**, 259.
13. van Hinsbergh V.W.M., van den Berg E.A., Fiers W., Dooijewaard G. (1990) Tumor necrosis factor induced the production of urokinase-type plasminogen activator by human endothelial cells. *Blood*, **75**, 1991.
14. Albini A., Melchiori A., Santi L., Liotta L.A., Brown P.D., Stetler-Stevenson W.G. (1991) Tumor cell invasion inhibited by TIMP-2. *J Natl Cancer Inst.* **83**, 775–779.
15. Sakon M., Monden M., Gotoh M., Kanai T., Umeshita K., Mori T., Trubouchi H., and Daikuhara Y. (1992) Hepatocyte growth factor concentrations after liver resection. *Lancet*, **339**, 818.
16. Kaneko A., Hayashi N., Tanaka Y., Ito T., Kasahara A., Kubo M., Mukuda T., Fusamoto H., and Kamaka T. (1992) Changes in serum human hepatocyte growth factor levels after transcatheter arterial embolization and partial hepatectomy. *Am J Gastroenterol*, **87**, 1014–1017.
17. Tomiya T., Tani M., Yamaka S., Hayashi S., Umeda N., and Fujiwara K. (1992) Serum hepatocyte growth factor levels in hepatectomized and nonhepatectomized surgical patients. *Gastroenterol.*, **103**, 1621–1624.
18. Rygaard K., Nakamura T., and Spang-Thomsen M. (1993) Expression of the proto-oncogene *c-met* and *c-kit* and their ligands, hepatoycte growth factor/scatter factor and stem cell factor, in SCLC cell lines and xenografts. *Br J Cancer*, **67**, 37–46.
19. Miyazaki M., Bai L., Taga H., Hirai H., Sato J., Namba M. (1991) Expression of liver-specific functions and secretion of a hepatocyte growth factor by a newly established rat hepatoma-cell line growing in a chemically-defined serum free medium. *Res Exp Med.*, **191**, 297–307.
20. Di Renzo M.F., Olivero M., Ferro S., Prat M., Bongarzone I., Pilotti S., Belfiore A., Costantino A., Vigneri R., Pierotti M.A. and Comoglio P.M. (1992) Overexpression of the c-MET/HGF receptor gene in human thyroid carcinomas. *Oncogenes*, 7, 2549–2553.
21. Prat M., Narsimhan R.P., Crepaldi T., Nicotra R.. Natali P.G. and Comoglio P.M. (1991) The receptor encoded by the human *c-MET* oncogene is expressed in hepatocytes, epithelial cells and solid tumours. *Int J Cancer*, **49**, 323–328.
22. Lotan R., Amos B., Watanabe H., and Raz A. (1992) Suppression of melanoma cell motility factor receptor expression by retinoic acid. *Cancer Res.*, **52**, 4878–4884.
23. El-badry O.M., Minniti C., Kohn E.C., Houghton P.J., Daughaday W.H., Helman L.J. (1990) Insulin-like growth factor II acts as an autocrine growth and motility factor in human rhabkomyasarcoma tumors. *Cell Growth Different*, **1**, 325–331.
24. Stracke M.L., Engel D., Wilson L.W., Rechler M.M., Liotta L.A. and Schiffmann E. (1989) The type I insulin like growth factor receptor is a motility receptor in human melanoma cells. *J Biol Chem.*, **164**, 21544–21549.
25. Di Renzo M.F., Narsimhan R.P., Olivero M., Bretti S., Giordano S., Médico E., Gaglia P., Zara P. and Comogho P.M. (1991) Expression of the MET/HGF receptor in normal and neoplastic human tissues. *Oncogene*, **6**, 1997–2003.
26. Kuniyasu H., Yasui W., Kitadai Y., Yokozaki H.. Ito H. and Tahara E. (1992) Frequent amplification of the c-MET gene in scirrhous type stomach cancer. *Biochem Biophys Res Commun.*, **189**, 227–232.
27. Liu C., Park M. and Tsao M.S. (1992) Overexpression of *c-met* proto-oncogene but not epidermal growth factor receptor or c-*erb*B-2 in primary human colorectoal carcinomas. *Oncogene*, **7**, 181–185.
28. Mondino A., Giordano S., and Comoglio P.M. (1991) Defective posttranslational processing actives the tyrosine kinase encoded by the MET proto-oncogene (hepatocyte growth factor receptor). *Mol Cell Biol.*, **11**, 6084–6–92.
29. Leone A., Flatow U., King C.R., Sandeen M.A., Margulies I.M.K., Liotta L.A. and Steeg P.S. (1991) Reduced tumor incidence, metastatic potential, and cytokine responsiveness of nm23-transfected melanoma cells. *Cell*, **65**, 23–35.
30. Leone A., McBride O.W., Weston A., Wang M.G., Anglard P., Cropp C.S., Goepel J.R., Lidereau R., Callahan R., Linehan W.M., Rees R.C., Harris C.C., Liotta L.A. and Steeg P.S. (1991) Somatic allelic deletion of nm23 in human cancer. *Cancer Res.*, **51**, 2490–2493.
31. Ayhan A., Yusui W., Yokozaki H., Kitadai Y., and Tahara E. (1993) Reduced expression of nm23 protein is associated with advanced tumor stage and distant metastases in human colorectal carcinoma. *Virch Arch B Cell Pathol.*, **63**, 213–218.
32. Cohn K.H., Wang F., DeSotoLaPaiz F., Solomon W.B., Patterson L.G., Arnold M.R., Weimar J., Feldman J.G., Levy A.T., Leone A. and Steeg P.S. (1991) Association of nm23-H1 allelic deletions with distant metastases in colorectal carcinoma. *Lancet*, **338**, 722–724.
33. Royds J.A., Stephenson T.J., Rees R.C., Shorthouse A.J. and Silcoks P.B. (1993) Nm23 protein expressin in ductal *in situ* and invasive human breast carcinoma. *J Natl Inst Cancer*, **85**, 727–731.
34. Nakayama T., Ohtsuru A., Nakao K., Shima M., Nakata K., Watanabe K., Ishii N., Kimura N. and Nagataki S. (1992) Expression in human hepatocellular carcinoma of nucleoside diphosphate kinase a homologue of the nm23 gene product. *J Natl Cancer Inst.*, **84**, 1349–1354.
35. Isoai A., Giga-Hama Y., Shinkai K., Mukai M., Akedo H. and Kumagai. (1990) Purification and characterization of tumor invasion-inhibiting factors. *Jpn J Cancer Res*, **81**, 909–914.
36. Isoai A., Goto-Tsukamoto H., Murakami K., Akedo H. and Humagai H. (1993) A potent anti-metastatic activity of tumor invasion-inhibiting factor-2 and albumin conjugate. *Biochem Biophys Res Commun.*, **192**, 7–14.
37. Isoai A., Giga-Hama Y., Shinkai K., Mukai M., Akedo H. and Kumagai H. (1992) Tumor invasion-inhibiting factor 2: Primary structure and inhibitory effect on invasion in vitro and pulmonary metastasis of tumor cells. *Cancer Res*, **52**, 1422–1426.
38. Shakoori A.R., Owen T.A., Shalhoub V., Stein J.L., Bustin M., Stein G.S. and Lian J.B. (1993) Differential expression of the chromonomal high motility growth proteins 14 and 17 during the on-set of differentiation in mammalian osteoblasts and promyelocytic leukemia cells. *J Cell Biochem*, **51**, 479–487.
39. Ikeyama S., Koyama M., Yamaoko M., Sasada R. and Miyake M. (1993) Suppresion of cell motility and metastasis by transfection with human motility-related protein (MRP-1/CD9) DNA. *J Exp Med*, **177**, 1231–1237.
40. Mohler J.L., Broskie E.N., Ranparia D.J., Sharief Y., Coleman W.B., and Smith G.J. (1992) Cancer cell motility-inhibitory protein in the Dunning adenocarcinoma model. *Cancer Res.*, **52**, 2349–2352.
41. Fazely F., Ledinko N. and Smith D.J. (1988) Inhibition by retinoids of *in vitro* invasive ability of human lung carcinoma cells. *Anticancer Res.*, **8**, 1387–1392.