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Review

Hepatocyte growth factor in invasive growth of carcinomas*

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Abstract. Hepatocyte growth factor is a multifunctional cytokine of the tumor microenvironment. An important advance in the knowledge of cancer progression has been the appreciation that the tumor invasive phenotype is strongly influenced by microenvironmental stimuli. Malignant tumor cells recruit vasculature and stroma through the production of growth factors and cytokines. The locally activated microenvironment (both cellular and extracellular elements) in turn modifies the proliferative and invasive behavior of the tumor cells. Hepatocyte growth factor accomplishes most of the functions of the invasive program in carcinomas (loss of adhesive junctions, motility, angiogenesis, survival/apoptosis), and may interact with other signals such as hypoxia. The purpose of the present review is to highlight examples of the progress in this area. The influence of hepatocyte growth factors on the carcinoma invasive phenotype is considered by evaluating the gene targets and the network of transcription factors activated in the specific responses.

Keywords. Hepatocyte growth factors, Met receptor, carcinoma invasiveness, tumor microenvironment, transcription factors, chemokine receptor, HIF-1α, E-cadherins/β-catenin.

1. Introduction

Cancer development is a multistep process during which genetic alterations confer specific types of growth advantage [1], but the tumor phenotype depends to a large extent on epigenetic mechanisms and changes in gene expression rather than on the initial mutations of oncogenes and oncosuppressors [2, 3]. All major aspects of cancer biology and behavior are, therefore, influenced by the tumor microenvironment and host selective pressure [4, 5]. Malignant growth and progression are characterized by several key changes: self-sufficiency of growth signals, insensivity to antigrowth signals, escape from apoptosis, unregulated proliferation potential, enhanced angiogenesis, invasiveness and metastasis formation [1]. Complex and redundant pathways involving the tumor cell and the microenvironment mediate tumor invasion at the primary site, survival and arrest in the bloodstream, and progressive outgrowth at a distant site. Understanding the molecular mechanisms responsible for these events and their dynamic interactions will help identify promising molecular targets for cancer therapy and key obstacles to their clinical development [6].

Role of hepatocyte growth factor in epithelial to mesenchymal transition and carcinoma invasiveness

Carcinoma is by far the most prevalent form of cancer, with 90% of all human malignancies of epithelial origin. Epithelia possess extensive junctional networks that physically separate the plasma membrane into apical and basolateral domains, promote adhe-

* This review is dedicated to Professor Aldo Bernelli-Zazzera.

sion and facilitate intercellular communication, thus restricting motility and permitting individual cells to function as a cohesive unit [7]. For most carcinomas, progression is accompanied by loss of epithelial differentiation and a shift toward a mesenchymal phenotype. This process, referred to as the epithelial to mesenchymal transition (EMT), exacerbates the motility and invasiveness of many cell types and is often considered as a prerequisite for tumor infiltration and metastasis. The diverse mechanisms that contribute to the EMT have been the subject of many reports and exhaustive reviews [8–10]. Many of these mechanisms involve growth factors that trigger various signaling cascades through their cognate receptor tyrosine kinases [11, 12]. For example, epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), fibroblast growth factor (FGF) and ephrins (EphA1, EphB1) promote cell growth, motility and survival in some cells, although to different extents under defined experimental conditions. The single biological functions played by each of these growth factors are cumulated in the hepatocyte growth factor (HGF), belonging to the family of soluble growth factors known as scatter factors (SFs) [13, 14]. HGF is a multifunctional cytokine able to orchestrate the various steps of the program called 'invasive growth', involving proliferation, disruption of intercellular junctions, migration and protection from apoptosis [12, 15–17].

Invasion can occur under physiological conditions such as embryonic development and tissue repair. Deregulation of this process is responsible for cancer invasiveness and consists in changes in tumor cell adherence to cells and to the extracellular matrix (ECM), proteolytic degradation of surrounding tissue and motility to physically propel a tumor cell through the tissue [18]. Most tumor cell movement in invasion is dynamic, involving the formation of adhesion to ECM at the leading edge of the cell, detachment from the ECM at the trailing edge and a ratcheting forward of the cell. The engagement of integrins, cell receptors for ECM components, accompanied by the recruitment of proteases to degrade the ECM is required. In addition to the destruction of ECM, proteases liberate embedded growth factors and chemokines, activate latent proteins on the cell surface and may serve protective roles in tumorigenesis [19–21].

Growth factors can stimulate motility and invasion through molecular mechanisms distinct from those involved in mitogenesis [22]. The HGF/Met receptor couple is an example, and this review focuses on the different molecular aspects played by HGF in carcinoma invasive growth. I shall consider the signaling pathways responsible for the activation of the transcriptional network after HGF/Met binding and the genes expressed downstream favoring the tumor invasive phenotype. Valuable Reviews on Met interaction with partner proteins (receptors and adhesive molecules) involved in invasive growth have recently appeared and are a useful complement to this monograph [23, 24].

2. HGF: a stimulus of the tumor microenvironment

HGF, a large, multidomain protein similar to plasminogen, consists of six domains: an amino-terminal domain, four kringle domains (K1–K4) and a serine protease homology domain, lacking enzymatic activity due to mutations in essential residues [25, 26]. HGF, synthesized as a single-chain, inactive precursor (pro-HGF), is converted proteolytically into a two-chain, active heterodimer, principally by a serine protease HGF-activator [27], and secondarily by plasminogen activators of urokinase (uPA) and tissue (tPA) types as well as by coagulation factors X, XI and XII [13]. So, although the biological activity of HGF depends solely on receptor binding, the factor has retained throughout evolution the architecture and mechanism of activation of the complex serine proteases typical of vertebrates. HGF also binds heparan sulfate proteoglycans with high affinity, which limits the diffusion of the factor *in vivo* but is not essential for receptor activation [13, 28]. HGF is a potent mitogen, motogen and morphogen for many kinds of epithelial cells, including hepatocytes, endotheliocytes, mammary and bronchial epithelial cells [29].

Under normal conditions, HGF is produced by cells of mesenchymal origin and the receptor Met, product of the c-*met* protooncogene, is expressed on epithelial cells [29–31]. In normal breast, for example, HGF is produced primarily by stromal cells, while epithelial cells express the receptor Met, but not HGF, thus creating a tightly controlled paracrine mechanism where localized expression of HGF regulates mammary ductal growth and differentiation [32]. Transcriptional regulation is very important in the restriction of HGF expression to mesenchymal tissues [33].

Dysregulation of HGF/Met couple in carcinoma cells

In contrast to what occurs in normal epithelia, HGF and Met are frequently overexpressed in invasive human breast carcinomas as well as in many other cancer types, and these autocrine loops are often associated with malignant progression of tumors and correlate with poor prognosis [34–39]. Met-positive tumor cells that do not produce HGF may nevertheless respond to HGF produced by stromal cells, as

occurs in poorly differentiated hepatocellular carcinomas [40, 41]. It is worth noting that Met can also be activated in an HGF-independent manner in tumors, particularly as a result of Met overexpression due to gene amplification, enhanced transcription or post-transcriptional mechanisms. In these cases, Met activation seems to depend on spontaneous dimerization and also on transactivation by other membrane receptors, such as EGF receptor, or cell/cell contact [39, 42, 43]. Abnormal processing of pro-HGF or the absence of normal negative regulators, such as cytosolic phosphatases, can also lead to constitutive Met activation and tumorigenesis. Missense mutations of Met have been identified in hereditary and sporadic papillary renal carcinomas and childhood hepatocellular carcinomas, gastric carcinomas and head and neck squamous cell carcinomas [39].

HGF and tumor stromal cells

Solid tumors are not just a mass of neoplastic cells, and carcinoma cells live in a complex microenvironment [6, 44]. The supporting players in the tumor microenvironment include stromal fibroblasts, infiltrating immune cells, the blood and lymphatic vascular networks and the ECM. Non-malignant stromal cells contained in carcinomas are able to influence tumor growth and progression positively or negatively [45]. These normal cells are coopted or modified by the cancer cells to produce a variety of growth factors, chemokines and matrix-degrading enzymes: autocrine and paracrine interactions are, therefore, important for carcinoma progression [6, 17]. For example, tumor angiogenesis is due in part to the secretion of vascular endothelial growth factor (VEGF) by tumors [46, 47], and is also mediated by cytokines, such as HGF and the chemokine CXCL12, produced by stromal cells such as activated fibroblasts [44, 48]. Carcinoma-associated fibroblasts (CAFs) have a well-recognized role in the carcinogenic process and exhibit gene expression profiles as well as biological characteristics distinct from those of normal fibroblasts. CAFs in fact exhibit the traits of myofibroblasts responsible for the synthesis, deposition and remodeling of much of the ECM in tumor stroma and produce paracrine cytokines and growth factors that influence the growth of carcinoma cells [44, 48]. CAF-secreted CXCL12 stimulates tumor proliferation and invasion directly by acting through the cognate receptor CXCR4, expressed on carcinoma cells such as breast cancer, promotes vasculogenesis by recruiting endothelial progenitor cells (EPCs) into carcinomas and may be involved in the recruitment of leukocytes, thus maintaining chronic inflammation that favors carcinoma growth by generating a tumor-prone microenvironment [4, 48, 49]. HGF is primarily expressed by fibroblasts in the tumor tissue, and the cognate receptor Met on the transformed epithelium. When signaling by the suppressive transforming growth factor-β (TGF-β) to stromal fibroblasts is lost, fibroblasts are stimulated to proliferate producing HGF, causing potential modifications in the ECM that are probably responsible for epithelial cell proliferation and transformation *in vivo* [44]. Thus, fibroblasts influence epithelial transformation by producing paracrine factors that affect both normal epithelia as well as carcinoma cells, but there is now considerable evidence that mutations arising in stromal fibroblasts can precede carcinoma development [17] Tumor-cell-conditioned medium induces fibroblast clustering, and the activation of the necrotic pathway in this cluster causes a massive (>200-fold) production of bioactive HGF responsible for carcinoma cell spread and invasiveness of a collagen lattice. This study seems to provide a molecular link and rationale between necrosis and enhanced tumor aggressiveness. Aggravated progression of tumors with necrotic foci may involve paracrine reciprocal signaling leading to stromal activation by direct cell-cell contact (so called nemosis) [50].

Cancer progression sees the interaction between HGF and hypoxia

Paradoxically, tumor progression is associated with both increased microvascular density and intratumoral hypoxia because newly formed vessels are imperfect and the tumor is a highly growing tissue that requires oxygen supply [51, 52]. Changes in cytokines (proinflammatory cytokines, chemokines and growth factors) produced by stromal cells and possible hypoxic niches in the tumor mass seem to influence the gene expression profile in malignancy and to determine cell fate. So, depending on the molecular context within the neoplastic cell and the external influences, specific patterns of molecular events take place with different outcomes in terms of their success at seeding to particular secondary sites [49]. For example, the hypoxic environment and the tumor-stroma interaction play an important role in pancreatic cancer progression [53]. Hypoxic stimulation accelerates the invasive activity of pancreatic cells (PK8), which is further enhanced when the hypoxic PK8 cells are cultured in the conditioned medium prepared from hypoxic fibroblasts (MRC5). MMP-2, MMP-7, MT1-MMP and Met expression increase in PK8 cells under hypoxia, and HGF secretion is enhanced in these hypoxic fibroblasts, leading to an elevation of Met phosphorylation in PK8 cells.

Stromal HGF production seems to correlate with the induction of HIF-1α, the regulatory subunit of hypoxia-inducible factor-1 (HIF-1) transcription factor,

which might participate in the expression of Met in cancer cells [54]. Likewise, hypoxia induces the transcriptional activation of the Met receptor and the subsequent amplification of HGF/Met signaling in tumors [55]. Thus, hypoxia-induced Met, sensitizing the cells to HGF, probably allows single neoplastic cells to escape hypoxia by invading surrounding tissue where oxygen and nutrients are not limited [18, 55].

3. Gene targets of HGF implicated in tumor invasiveness

A large body of experimental evidence has demonstrated that HGF and Met play a critical role in the invasive growth of tumor cells, a hallmark of metastatic cancer [56]. This complex program, including the loss of cell-cell adhesion, cell migration, invasion through the basement membrane into the connective tissue, survival and arrest in the bloodstream and colonization of distant tissues [9–11], is supported by a unique Met-receptor-associated signaling apparatus as well as by the modulatory association with partner proteins, namely α6β4 integrin, plexin B1 and CD44, and other receptor tyrosine kinases (RTKs) [23, 57]. In addition, HGF stimulates migration of oral squamous cell carcinoma cells through the initial recruitment of integrins (β1), cytoskeletal proteins and $p125^{FAK}$ into the focal adhesion that is dependent on tyrosine kinase activity [58], and enhances HuCCA-1 cholangiocarcinoma cell proliferation and invasion by mediating FAK and Src phosphorylations [59].

Below, I discuss the data regarding the signaling pathways and the genes induced downstream of activated Met.

Cell-cell adhesion in carcinomas and changes in E-cadherin expression by HGF

Malignant transformation and tumor progression are often characterized by major changes in the organization of the cytoskeleton, decreased adhesion and aberrant adhesion-dependent signaling. Loss of cell-cell adhesion followed by dissociation of epithelial structures is a prerequisite for increased cell motility and tumor invasion. This disruption of adherens junction assembly may be achieved by downregulation of the expression of cadherin or catenin family members or by the activation of signaling pathways that prevent the assembly of the adherens junction, as occurs after HGF treatment [60–65]. In carcinomas, germline or somatic mutations of the CDH1 gene for E-cadherins or hypermethylation of the CDH1 promoter may be observed. By binding to specific DNA sequences in the E-cadherin promoter, Snail represses E-cadherin transcription. Snail upregulation by HGF, mediated by the MAPK/Egr-1 signaling pathway, seems therefore to be involved in HGF-induced hepatoma cell scattering, migration and invasion [66]. Through dynamic recycling of E-cadherin, the E3 ubiquitin-ligase Hakai can also modulate cell adhesion. HGF, by enhancing tyrosine phosphorylation directly via Met or indirectly via c-Src, may favor E-cadherin-Hakai interaction and/or the subsequent dissociation, ubiquitination and degradation of E-cadherins in the proteasome [64, 65]. We have demonstrated that in breast carcinoma but not in normal epithelial cells, HGF increases Met-E-cadherin coimmunoprecipitation and coendocytosis, favoring phosphorylation of β-catenins. As described below this mechanism may be important for the regulation of β-catenin/Tcf signaling in tumors [67].

HGF regulates the expression of matrix metalloproteinases and the plasminogen activation system for carcinoma invasiveness

Malignant epithelial tumors grow beyond the basement membrane and invade the surrounding ECM through processes involving proteolytic degradation mediated by matrix metalloproteinases (MMPs) and the plasminogen activation system [68, 69]. HGF may induce this proteolytic network in carcinoma cell lines as well as in clinical tumors, explaning some aspects of invasiveness. MMPs, a family of Zn^{2+}- and Ca^{2+}-dependent endopeptidases, are able to degrade almost all ECM proteins. MMP-2 and MMP-9 degrade components of the basement membrane (collagen IV and laminin) but also fibrillar collagens, after their initial degradation by collagenase. In contrast to MMP-2, that is constitutively expressed, MMP-9 levels are usually low, and enzyme expression is induced, for example by TGF-β, EGF, HGF and tumor necrosis factor (TNF)-α. Breast cancer cells induce stromal fibroblasts to express MMP-9 via secretion of TNF-α and TGF-β, a process modulated by HGF [68]. Invasion of ovarian cancer cells is associated with HGF, and requires $p70^{S6K}$-mediated MMP-9 expression [70]. The induction of MMP-1, -3, and -7 genes in human hepatocellular carcinomas by HGF is mediated by the Ets-1 transcription factor [71]. In clinical breast cancer, membranous and cytosolic MT1-MMP (known as MMP14) is highly expressed in aggressive tumors and is associated with poor clinical outcome. Reduction of MT1-MMP from breast cancer cells resulted in significant decrease of *in vitro* invasiveness and loss of response to the invasion stimulus, HGF [72].

In a variety of cell types, the glycolipid-anchored urokinase receptor (uPAR) is localized pericellularly with components of the plasminogen activation system and endocytosis receptors. uPAR is also coex-

pressed with caveolin, G-protein-coupled receptors (GPCRs) and members of the integrin adhesion receptor superfamily. The formation of functional units with the various proteins allows uPAR to mediate the focused proteolysis required for cell migration and invasion and to contribute both directly and indirectly to cell adhesive processes in a non-proteolytic fashion. This dual activity, together with the initiation of signal transduction pathways by uPAR, is believed to influence tumor progression/metastasis [73]. Against expectations, increased levels of plasminogen activator inhibitor-1 (PAI-1) are also predictive of a poor prognosis for the survival of patients with cancer, and the absence of PAI-1 in mice impaired tumor growth and angiogenesis in malignant and inflamed tissues [69]. The balance between uPA-uPAR and PAI-1 determines the angiogenic outcome in terms of integrin-dependent endothelial adhesion and migration [69].

HGF might influence different adhesive and non-adhesive functions of the plasminogen activation system, also controlling signal transduction pathways involved in tumor growth and angiogenesis. We have observed that HGF activates uPA and PAI-1 promoters in HepG2 hepatocarcinoma cells, and HIF-1 is involved in the transactivation. PI3K/JNK1 transducers play a role in HGF-dependent uPA and PAI-1 gene reporter activation via HIF-1. This was the first evidence for gene targets of HGF regulated through HIF-1 activity [64, 74]. Previous studies had shown the involvement of Ets-1 and AP-1 in the activation of the uPA promoter by HGF [75, 76]. We also demonstrated that HGF is additive to hypoxia in increasing uPA and PAI-1 promoter-vector activities [74]. The importance of our findings in relation to the role of HGF in invasive growth and tumor progression is discussed below, taking into consideration that human breast carcinoma cells promote angiogenesis, both providing and enhancing uPA and PAI-1 expression in endothelial cells [77]. HGF stimulates the uPA/uPAR proteolytic network in prostate and stomach cancer cells, which may be important for acquisition of invasive potential [78, 79]. It is possible that HGF-dependent activation of Met and uPAR is involved in IGF-1-mediated migration and invasion [80].

Chemokine receptor expression is regulated by HGF

The ability of tumor cells to metastatize, i.e. to spread to other parts of the body, is perhaps the main reason why certain types of cancer are often fatal. But how tumors acquire this characteristic? Genotypic as well as gene expression changes are known to be involved. Growth factors, chemokines (chemotactic cytokines) and hypoxia present in the microenvironment where the tumor grows play key roles in these regulatory mechanisms and influence different steps in the invasive/metastatic processes [81, 82]. Cancers have a complex chemokine network that may influence leukocyte infiltration and angiogenesis [49, 83]. Inflammatory cytokines induce chemokine production by epithelial tumor cells, and the macrophages that express the corresponding receptor bind the chemokine and undergo a rapid cytoskeletal rearrangement. Restricted expression of chemokine receptors on leukocytes may allow control of movement and retention at the tumor site as well as induction of the transcriptional programme that favors cell migration, such as the induction of MMPs, and cell survival [49]. Malignant cells can also express chemokine receptors and respond to chemokine gradients, and this may be related to the growth and spread of cancers that originate from the ovary, colon, prostate or breast. Different cancers express some CC and CXC chemokine receptors, and the corresponding ligands are sometimes produced at the sites of tumor spread [49, 83]. Malignant cells from at least 23 different types of human cancer of epithelial, mesenchymal and hemopoietic origin express the chemokine receptor CXCR4 and respond to its ligand CXCL12. The latter chemokine is found in primary tumor sites in ovarian and pancreatic cancers as well as in glioma and lymphoma, and at sites of metastases in breast and thyroid cancer, neuroblastoma and hematological malignancies. Expression of CXCL12 in primary tumors could therefore be expected to retain the tumor cells at this site, which would encourage growth and survival and discourage invasion and metastasis. However, this is likely to be a dynamic process. In some cases, protease production could degrade CXCL12 and local conditions could increase expression of the receptor [49].

The large production of CXCL12 in lymph nodes, lungs, bone and liver has suggested that this distribution could contribute to the tropism of breast cancer metastases for these sites. Despite the involvement of CXCR4 in the metastatic process, however, the studies do not distinguish between the role of CXCR4 in the arrest of tumor cells in the endothelium and extravasation into target tissues, or initial survival, growth, vascularization and invasiveness within target tissue. For prostate cancer, CXCR4 seems to be involved in tumor growth, angiogenesis and metastatic potential [84].

Using low (MCF-7) and highly (MDA-MB231) invasive mammary tumor cells, we observed for the first time that HGF affected CXCR4 gene expression in an opposite manner in the two cell lines [85]. HGF induced CXCR4 and tumor invasiveness through Matrigel-covered membranes in MCF-7 cells, but reduced CXCR4 expression and constitutive invasive

capacity in MDA-MB231 cells. These opposite effects seem to be specific for CXCR4 because CCR7, coexpressed in these malignant cells, is enhanced after HGF in both the cell lines even if with different time-courses (unpublished data). Studies are in progress in my laboratory to deepen our knowledge of the regulatory mechanisms involved in CXCR4 expression, with the purpose to clarify the steps of the breast tumor metastatic process involving an HGF-dependent regulation of CXCR4. The enhancement of CXCR4 under HGF stimulus may be important for the recruitment of circulating neoplastic cells to distant sites ("homing hypothesis") and possibly for the spreading within target tissues where HGF is produced by stromal cells. In the acquisition of the metastatic phenotype, hypoxia probably plays a cooperative role. We hypothesize that at the primary site of tumor growth, CXCR4 may be induced by hypoxia- or oncogene/oncosuppressor-dependent HIF-1 activation, while homing is probably related to HGF production in the target tissue of metastasis [51, 85, 86]. In fact, HGF and hypoxia are not additive for CXCR4 induction, and different transduction pathways, i.e. ERK1/2 and PI3K, respectively, are mainly triggered by the two stimuli, supporting the idea that HGF and hypoxia may act in different steps of tumor cell invasiveness [85]. The reduction in CXCR4 expression observed in highly invasive breast cancer cells (MDA-MB231) may favor tumor cell retention at the secondary site, where HGF is produced by stromal cells together with CXCL12 [44, 48]. Other growth factors, such as VEGF, are likely to play a different role and seem to affect invasiveness of MDA-MB231 cells in an autocrine manner through enhancement of CXCR4 expression [87].

The data reported above remind us that the microenvironment influences the expression of malignancy, and gene expression profiles (especially in microdissected cancer cell alone) cannot give the full picture nor inform us about the signaling pathways that may be differently activated depending on the spectra of genes expressed by both tumor and stroma [88]. Progression from normal to malignant phenotype involves aberrations in the reciprocal interactions of multiple cell types with each other and with other components of the microenvironment. Thus, targeted therapies delivered to the tumor may need to include drugs targeted not only to the tumor, but also to other cell types in the tumor microenvironment [82]. Manipulation of the tumor chemokine network and HIF-1 activity, by targeting the HGF/Met system, might have a therapeutic potential in malignant diseases [17, 49, 51, 89, 90].

4. Network of transcription factors activated by HGF: possible role in tumor progression

HGF and hypoxia converge on HIF-1 activation: role in angiogenesis and apoptosis

The molecular mechanisms underlying the interactions between stromal and tumor compartment are only poorly understood, although growth factors are known to control this complex interplay tightly [91]. HIF-1 transcription factor may play a key role in this intricate network of signals, by influencing the angiogenic and the apoptotic processes important for tumor survival, growth and progression [6, 51].

The mechanisms involved in HIF-1 activity regulation are different in normoxia and hypoxia: effect of HGF in normoxic cells. HIF-1 is a heterodimeric transcription factor formed by an inducible α and a constitutive β subunit [51]. Stimuli of the tumor microenvironment, such as hypoxia and HGF, may induce HIF-1α [54, 92]. Furthermore, oncogene gain-of-function and tumor suppressor gene loss-of-function, depending on the signal transduction pathways that are active in a particular tumor cell, enhance HIF-1α protein level leading to HIF-1 activation [92]. HIF-1 transactivates a vast array of gene products controlling angiogenesis/neovascularization, energy metabolism, survival, pH and cell migration, and has been recognized as a strong promoter of tumor growth [51, 93]. HIF-1α overexpression confers selective advantages that contribute to the accumulation of mutations during tumor progression, and it is considered, therefore, a marker of aggressive disease in several tumor types. In breast and cervical cancers, HIF-1α immunohistochemistry identifies a subset of patients at increased risk of treatment failure and death, despite the histological classification of their tumors as low grade [51].

Thus, growth factors and hypoxia converge on induction of HIF-1α even if the mechanisms involved are different (Fig. 1). Under normoxic conditions, HIF-1α is maintained at low levels because of VHL-dependent HIF-1α proteasomal degradation, while hypoxia enhances HIF-1α level via stabilization. Other oxygen-dependent post-translational mechanisms regarding the α subunit seem to influence HIF-1 activity negatively. These are the cooperative binding VHL-FIH-1 (factor binding HIF-1), a corepressor which recruits histone deacetylase to HIF-1α under normoxic conditions, and Asn803 hydroxylation, which prevents coactivator p300 binding [51].

HGF, through Met binding, seems to be the only growth factor that regulates HIF-1α expression at the transcriptional level, as demonstrated both in HepG2 hepatoblastoma and MCF-7 breast carcinoma cells

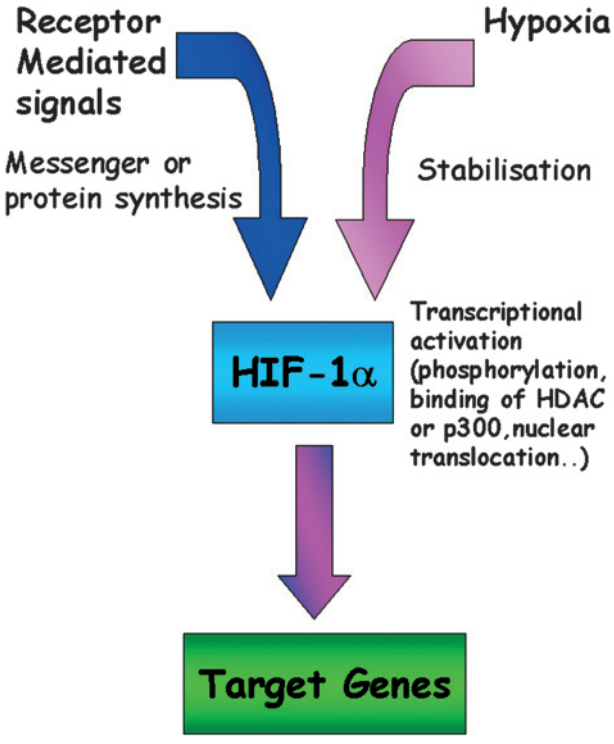

Figure 1. Regulation of HIF-1 under normoxic (receptor mediated signal) and hypoxic conditions.

under normoxic conditions [54, 85]. HGF-dependent NF-κB activity controls HIF-1α transactivation, and thus an autoregulatory loop is probably triggered in carcinoma cells due to the hypoxia-responsive elements (HREs) in the HIF-1α promoter. This mechanism of regulation does not occur in MDA-MB231 breast cancer cells, where HIF-1β is mutated and the functional transcription factor cannot be assembled. The HGF-dependent regulation of HIF-1α expression by NF-κB is mainly at the level of the 5′ untranslated region (5′UTR), which may play an important role in α subunit transcription [94].

HIF-1 is the master regulator of oxygen homeostasis, and NF-κB is a redox-sensitive factor [51, 95], and both play a key role in the link between inflammation and cancer [51, 96]. Aberrant activation and nuclear localization of NF-κB in cancer is common [97]. The pro-inflammatory cytokines [interleukin-1 (IL-1) and TNF-α], gene-targets of NF-κB [96], also regulate HIF-1: IL-1-mediated upregulation of HIF-1α via an NF-κB/COX2 pathway identified HIF-1 as a critical link between inflammation and oncogenesis [98, 99]. Reactive oxygen species (ROS) can induce pro-inflammatory cytokines, and as a consequence, HIF-1 activation determines the cellular response to oxidative stress. IL-1α and -β induce HGF [100], and ROS-sensitive mechanisms may be involved downstream of Met [57].

HIF-1 transactivating activity undergoes further regulatory mechanisms, but the potential signaling mediators have still to be unraveled. As regards HGF, we have shown that *N*-acetyl-L-cysteine, an antioxidant, reduces the stimulatory effect of HGF on stress kinase activities, while MAPK (p42/44) was unmodified, suggesting the involvement of c-Jun-terminal kinase-1 (JNK1) and MAPK (p38) in HIF-1 activation. Of note, the LY294002 inhibitor of PI3K activity, one of the principal transducers of HGF/Met receptor signaling, prevented HIF-1 DNA binding and JNK1 activity, but the inhibition of MAPK (p42/44) with PD98059 was ineffective. We hypothesize, therefore, that HGF may trigger a signal transduction cascade involving PI3K/JNK1, ultimately leading to HIF-1 activation [54]. The role played by JNK1 in HGF-treated carcinoma cells seems to be the direct phosphorylation of NF-κB, regulating HIF-1α transcription [94]. IGF-1, insulin and EGF also stimulate HIF-1α protein expression through receptor-mediated signals, but at the post-transcritional level in colon and prostate cancer cells [101, 102]. The receptor signaling pathways triggered by IGF and EGF, and regulating HIF-1α expression, involve PI3K/Akt/FRAP and Ras/MEK/MAPK/eIF-4E [101–104]. Translation of HIF-1α is particularly sensitive to growth factors that activate mammalian target of rapamycin (mTOR), such as IGF. mTOR is a serine/threonine protein kinase that phosphorylates a series of substrates involved in protein translation [90, 101]. Moreover, the early stabilization of HIF-1α by hypoxia seems to depend on PI3K/Akt, whereas prolonged hypoxia results in inactivation of Akt and activation of GSK3β, which down regulates HIF-1 activity by preventing protein α subunit accumulation [105].

Role of HGF in the angiogenic process. The angiogenic process, critical for solid tumor growth as well as metastatic dissemination, involves proteolysis of pericellular and extracellular matrix to create a pathway for the passage of proliferating, migrating and apoptosis-resistant endothelial cells. Several excellent reviews have summarized the process of angiogenesis, its regulation by growth factors and proteases and its contribution to tumor growth and progression [106–109]. Recently, circulating EPCs have been proposed to give rise to new vessels (neovascularization) in tumors [110]. HIF-1 controls the expression of the angiogenic factors VEGF-A and angiopoietin-2 [111, 112] as well as the activation of the plasminogen/plasmin system, which is the most powerful enzymatic system used by endothelial cells in the extracellular proteolytic process to promote tumor angiogenesis [77, 93].

However, both HGF (possibly produced by tumor and stromal cells) and CXCL12 of stromal origin are

recognized as angiogenic factors by activating EPCs or endothelial cells in tumor tissue, such as breast carcinomas [44, 48, 109]. Numerous studies have shown that HGF is a potent angiogenic factor *in vivo* in normal human tissues, tumors and derived xenografts. To determine whether HGF can modulate the *in vivo* growth of human breast cancers within a natural mammary environment, Lamszus et al. [113] studied the orthotopic growth of HGF-transfected versus control clones of MDA-MB 231 cells in the mammary fat pads of athymic nude mice. HGF-transfected tumors had significantly higher tumor microvessel density than control tumors. Moreover, there were much higher titers of chemotactic activity for microvascular endothelial cells in cell-conditioned medium and primary tumor extracts from HGF-transfected clones as compared with control clones. Other studies used loss-of-function approaches to demonstrate the role of endogenous HGF in *in vivo* angiogenesis. Kuba et al. [114] showed that inhibiting HGF leads to a dramatic decrease in microvessel density in mammary carcinoma xenografts.

The role of HGF in tumor angiogenesis needs further study, but it is clear that HGF may act both directly and indirectly. The pathways hypothesized until now for the angiogenic role of HGF are reported in Fig. 2. Met is expressed by tumor microvessels *in vivo*, and systemic blood levels of HGF are frequently elevated in tumor-bearing patients and correlate with tumor microvessel density. HGF is expressed and secreted by a wide variety of tumor cells and by vascular smooth muscle cells, pericytes and fibroblasts, activating endothelial Met receptors in a paracrine fashion [50, 109]. HGF strongly induces DNA synthesis and proliferation in vascular endothelial cells of various origins, processes requiring MAPK/ERK and STAT3 activation, enhances endothelial cell survival and renders vascular endothelial cells resistant to apoptosis induced by various conditions including serum deprivation and hypoxia, and promotes motility of neuromicrovascular endothelial cells [109]. HGF can also affect angiogenesis, regulating the expression levels of other well-known proangiogenic and anti-angiogenic factors such as VEGF, IL-8 and thrombospondin 1. HGF has been shown to induce VEGF mRNA and protein expression in normal and neoplastic cells, as well as the expression of the receptor flk-1 in an endothelial cell line [109]. The contribution of VEGF to HGF-induced angiogenesis was found to be either additive or synergistic, depending on the cell/tissues examined [115]. In the human breast cancer cell line MDA-MB231, HGF mediated angiogenesis through positive VEGF and negative thrombospondin 1 regulation [116]. The role of HIF-1 in the control of VEGF expression in tumor and endothelial cells in response to HGF, and whether an inverse regulation may occur, has not been studied. The enhancement of the plasminogen activation system by HGF through HIF-1 transcritional activity may thus play a role not only in breast tumor invasiveness but also in angiogenesis [54, 77]. Most of the HGF-induced urokinase is bound to uPAR on the cell surface, where it is well positioned to mediate focal degradation of ECM proteins, a prerequisite for cell invasion [109].

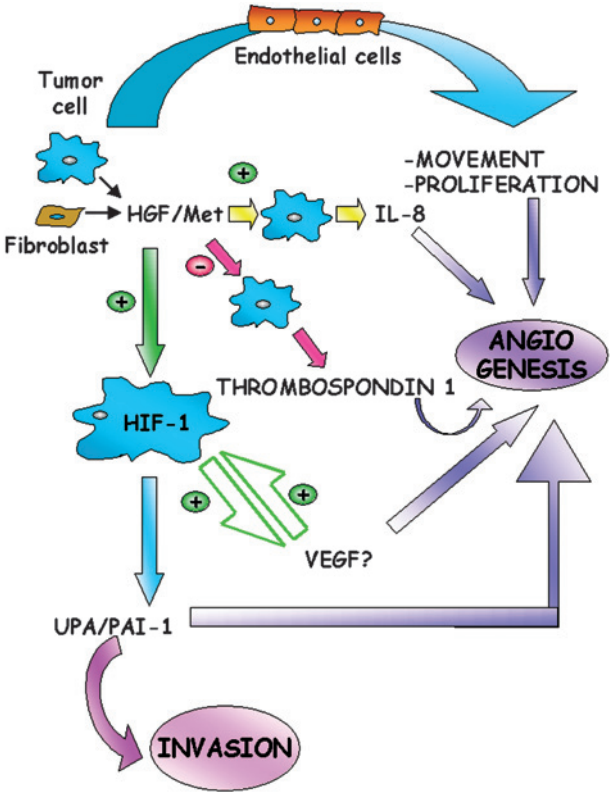

Figure 2. Role of HGF in tumor angiogenesis.

HGF and apoptosis. One interesting role of HIF-1 activity may be the protection of hepatic carcinoma cells from apoptosis caused by HGF. In fact, while HGF in general protects tumors from apoptosis induced by chemotherapeutic drugs and DNA-damaging agents [117, 118], in some human and mouse liver tumor cells, HGF is pro-apoptotic [119–121]. Thus, we decided to evaluate the involvement of HIF-1 in the extrinsic apoptotic pathway triggered by HGF using wild-type (c1c7) and the β-subunit-mutated (c4) mouse hepatoma cell lines. These carcinoma cells were differently susceptible to apoptosis induced by HGF, and the c4 cells underwent apoptosis (40 %) 48 h after HGF treatment, i.e. well before and to a larger extent with respect to c1c7 cells. The revertant vT{2} cells, consisting of c4 cells stably transfected with

HIF-1β expression vector, behaved as the parental cells. The pro-apoptotic effect of HGF in c4 cells lacking HIF-1 activity is probably related to the loss of cytoprotective and signaling functions. We observed that JNK1, caspase 8 and 3 activities persistently increased, while c-Myc, p53 and ornithine decarboxylase protein levels progressively decreased in HGF-treated c4 cells. These molecular patterns are profoundly different from those of c1c7 cells. Lack of HIF-1 activity may contribute to the triggering of the extrinsic apoptotic pathway by HGF, consisting of caspase 8 activation, BID cleavage and cytochrome c release, concomitant with caspase 3 activation [121]. In ovarian cancers, the pro-apoptotic effect of HGF is additive to that of cisplatin and paclitaxel and requires p38 MAPK [122].

The strong correlation between HIF-1α expression, alone or in combination with p53 and BCL2, and increased patient mortality, as well as the role of HIF-1 as a promoter of early invasive lesions, suggest this transcription factor as a promising therapeutic target in cancer [51]. The finding of the susceptibility related to HIF-1 activity for HGF-induced hepatoma apoptosis underlines the importance to inhibit this transduction pathway and influence the pro-apoptotic effect of HGF.

NF-κB and Ets-1 activated by HGF control different steps of tumor cell dissemination and homing

Regulation of the expression of specific genes involved in cell dissemination and homing in cancers might depend on (i) the consensus sequences for the transcription factors and their relative positions on the promoter, as well as the abundance of transcriptional cofactors; (ii) the cell signaling pathways that are interconnected and form a complex signaling network and (iii) the information received from growth factor receptors, cell-matrix, cell-cell contacts and other niche signaling such as hypoxia. Understanding how these extraordinarily complex signaling networks function *in vivo* and how they are altered in cancer cells represents a major intellectual challenge [123, 124].

The most recent HGF target gene that we have identified is the CXCR4 chemokine receptor that undergoes a completely different regulation in low and highly invasive breast carcinoma cell lines. In addition, the transcription factors involved in CXCR4 induction vary depending on HGF or hypoxia exposure. The CXCR4 gene promoter (−2632/+86) was examined: within 700 bp upstream the TATA box, six consensus sequences for Ets1 (5′-GGAA/T-3′) and one NF-κB consensus site called 'p65' (5′-CCTGGGCT**TCCC**AAG-3′) were found. Three forward HRE sites (5′-CGTGC/T-3′) and two reverse HRE sites (5′-GCACG-3′) were upstream between −825 and −1933 bp [125].

The Ets1 transcription factor target genes include invasion and metastasis-related genes, such as MMPs and osteopontin. Thus, it is not surprising that the aberrant expression of Ets1 target genes contributes to malignant transformation and tumor progression [126]. Ets1 undergoes a complex regulation including synergism with other transcription factors, interaction with acetyl transferases and phosphorylation [127]. Sequences flanking the central core influence the binding specificity: for the CXCR4 promoter, the NF-κB consensus site is near the cluster of Ets1-binding sequences. We observe that in HGF-treated MCF-7 cells (low invasive carcinoma cell line), CXCR4 protein induction and cell invasiveness require NF-κB and Ets1 activation. These two transcription factors probably cooperate, because the blockade of NF-κB prevents Ets1 DNA binding. The MEK1/ERK1/2 transduction pathway is involved in Ets1 binding to the CXCR4 promoter. In hypoxic MCF-7 cells, CXCR4 was induced principally through HIF-1 and partly by NF-κB, while Ets-1 was ineffective [125]. These data confirm the role of NF-κB in tumor progression mediating the influence of the tumor microenvironment on cell invasiveness.

Studies are in progress to understand the mechanisms underlying the inhibitory effect of HGF on CXCR4 expression in MDA-MB 231 cells (highly invasive carcinoma cell line) [85]. It has recently been shown that the amount of CXCR4 is higher in human primary breast tumors than in the lymph node metastases. One of the mechanisms involved seems to be a CXCL12-mediated degradation of CXCR4 and lower HIF-1α levels [128].

Tcf/Lef activity downstream of HGF/Met: possible role in carcinoma growth and progression

The acquisition of the invasive phenotype by epithelial tumor cells requires the disruption of intracellular adhesion junctions and the expression of genes involved in cell cycle progression (c-*myc* and cyclin D1) and proteolysis (MMPs) [129]. E-cadherins may be considered signal-transducing molecules through interaction with receptor and non-receptor tyrosine kinases and regulation of β-catenins [61, 62, 64, 130]. Both constitutive activation of the Wnt signaling pathway in some tumors like colon cancer, as a consequence of mutations of APC, β-catenin and axin/conductin, or activation of an alternative Wnt pathway, for example by HGF in breast cancer, have been reported [61, 67, 131]. In MCF-7 breast carcinoma cells treated with HGF we have demonstrated that E-cadherins colocalise and coimmunoprecipitate with Met, and that E-cadherins are phosphorylated prob-

ably playing a functional role in the amplification of the signal downstream of Met. Consistent with the literature [64], we hypothesize that E-cadherin may be phosphorylated by Met tyrosine kinase or c-Src tyrosine kinase [67]. After HGF treatment, β-catenins also coimmunoprecipitate with E-cadherins and are tyrosine phosphorylated [67]. E-cadherins seem to acquire the capacity to sequester a transcriptionally competent, probably phosphorylated pool of β-catenins [132]. Due to a change in conformation, tyrosine-phosphorylated β-catenins decrease the affinity for axin, a step required for ubiquitination and proteasomal degradation [133]. These amplification reactions have not been observed in normal MCF-10 epithelial cells, in which Met and E-cadherins do not coimmunoprecipitate/colocalize after HGF treatment [67].
In MCF-7 cells, the presence in the Met complex of E-cadherins as well as β-catenins does not restrain but probably facilitates β-catenin phosphorylation by the Met tyrosine kinase signaling pathway, followed by nuclear translocation, as compared with HGF-treated MCF-10 cells. In the nucleus, β-catenins lead to activation of the Tcf/Lef transcription factor [67]. We have demonstrated that c-Src is along a common signaling pathway triggered by HGF/Met in MCF-7 cells and involved in Tcf/Lef activation. Moreover, the blockade of c-Src and PI3K completely prevented the activity of TOPFLASH, a gene reporter driven by a multimer of the Tcf/Lef consensus sequence [67]. In normal HGF-treated rat hepatocytes, lacking E-cadherin association, β-catenins are directly phosphorylated by Met [134]. In metastatic human colon carcinoma cells, β-catenins are associated with constitutively activated Met and are phosphorylated, leading to Tcf/Lef transactivating activity. Sensitivity to HGF is observed only in low-aggressive colon carcinoma cells [135]. Wnt signaling regulates the expression of Met in colorectal cancer [136]. In normal mammary epithelial cells of the mouse, HGF decreases GSK3β activity, responsible for Ser phosphorylation of β-catenins and their degradation, thus favoring nuclear accumulation of β-catenins and gene expression [131]. In β-catenin transgenic mice, HGF-induced hepatomegaly seems to be due to activation of the Tcf/Lef signaling pathway [137].

Notch signaling and the negative regulation of Met-dependent invasive growth

Notch receptors and ligands are expressed on the cell surface and enable the interaction between adjacent cells upon receptor-ligand binding. Notch signaling molecules have an important well-documented role in vascular development, differentiation, proliferation, apoptosis, tumorigenesis and angiogenesis [138]. A complex interrelation occurs between Met and Notch signaling pathways. Met activation leads to transcriptional induction of Notch function, i.e. sprouting of the tracheal tree, through transcriptional induction of the ligands Delta 1 and 4. Notch may limit HGF activity through repression of the Met oncogene, a mechanism possibly involved in the negative regulation of invasive growth [139]. It would be interesting to evaluate the role of the regulatory loop on tumor angiogenesis. Notch activity increases specifically in tumor endothelium and in various tumor types, and the Notch signaling pathway may mediate communication between various cell types in the tumor microenvironment [138].

5. Interaction of the HGF receptor Met with other membrane and intracellular molecules: importance of endocytosis for signaling

The complexity of the control mechanisms conferring an invasive phenotype in tumors is becoming more and more evident. The specificity of biological responses may depend not only on the intrinsic characteristics of the Met receptor (through a unique modulation of the signaling kinetics or the combined activation of a coordinate set of transducers), but also on the cell context through the interaction with other receptors (RTK and GPCR) [57]. EGF receptor (EGFR) signal transactivation induces MMP-mediated ectodomain shedding of Met, and aberrant EGFR activation elevates Met expression and phosphorylation in thyroid carcinoma cells [140]. GPCR and EGFR may transactivate the protooncogenic Met tyrosine kinase in pancreatic and hepatocellular carcinoma cells. This transactivation process involves the acute production of ROS by the membrane-bound NADPH oxidases [57].
In certain conditions and depending on the cell type, Met signaling outputs may be modulated by interactions with other transmembrane proteins, namely the α6β4 integrin, pexin B1 and CD44. This topic is the subject of an interesting review [23]. The result of these interactions is to create a wider docking platform, enhancing Met oncogenic potential and pro-invasive and metastogenic activity of HGF as in the case of α6β4 integrin. CD44 seems to be necessary for Met signaling-activation in certain cell types, through particular protein association, such as ezrin.
To complete the scenario, different endocytic routes orchestrate biochemical pathways and biological behavior. As recently reported, endocytosis may be considered ‘ fundamental organizer of the cell, which coordinates the core variables in cell signaling - duration, intensity, integration, and spatial distribution – to control such processes as cell fate determi-

nation and cell migration' [141]. Upon HGF stimulation, Met is rapidly internalized via clathrin-coated vesicles and traffics through an early endosome compartment. This pathway seems essential for HGF/Met to trigger the ERK response, is controlled by PKCε and may be a link between endocytosis and cell signaling. Post-early endosomal Met traffic along microtubules towards perinuclear compartments (including, in part, the Golgi apparatus) is positively regulated by PKCα, and concerns the newly synthesized precursor form and, to a lesser extent, internalized recycling Met. Thus, dual pathways impinge on the Met response controlling the localization of the receptor, and the strength and location of signal output that may be important for HGF-dependent cell migration [142].

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