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The biological role of HGF-MET axis in tumor growth and development of metastasis

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1. ABSTRACT

Hepatocyte growth factor (HGF) and its receptor MET play an important role in cancer growth and metastasis. Activation of MET elicit multiple cellular responses regulating cell survival, morphogenesis, adhesion, migration, breakdown of extracellular matrix (ECM) and angiogenesis. Numerous disorders related to deregulation of HGF-MET axis have been reported. Thus, new therapeutic agents targeting HGF-MET signaling have been sought. Here, we will present data describing the role of HGF-MET axis in growth and metastasis of tumor cells together with the recent approaches to block this axis.

2. INTRODUCTION

Oncogenes encode proteins with broad range of biological activities that play important role in both triggering oncogenic transformation and maintaining the cancer phenotype (1). Oncogenes control various cellular processes related to tumor cells growth and metastasis therefore silencing of single oncogene may lead to tumor regression. Hence, extensive studies have been performed in order to find a way to interfere with their functions.

MET oncogene encodes tyrosine kinase receptor for hepatocyte growth factor (HGF). MET is produced as a propeptide and subsequently cleaved into two chains: 70 kDA alpha-chain and 140 kDA beta-chain. Mature protein is composed of three important regions: N-terminal, semaphorin and kinase domains (Figure 1). Interactions between HGF and its receptor have been shown to be essential for mammalian embryogenesis, mainly muscle development, nervous system formation, hematopoietic cells differentiation, bone remodeling and angiogenesis (2). HGF and MET knock-out mice die in early embryonal stages, because of abnormal placenta development. Furthermore, these deficient embryos develop numerous liver, muscle and neuronal defects. Liver is reduced in size and shows extensive loss of parenchymal cells (3). Muscles derived from migratory precursors e.g. muscles of the limbs, diaphragm and tip of tongue are absent, while the axial skeletal muscles are present (4). Moreover, MET activation has a crucial role in epithelial-mesenchymal interactions during acute injury repair. MET mediates epithelial cells dissociation, migration towards the damaged site, proliferation and reconstitution of epidermal layer.

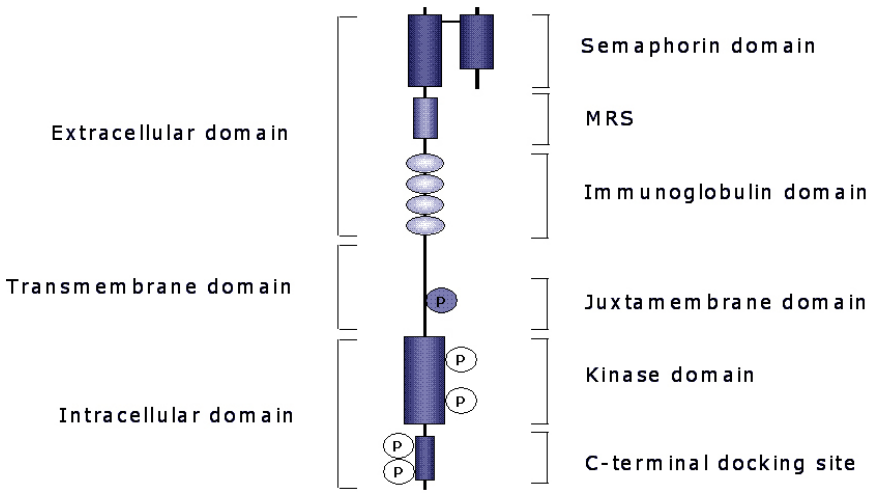

Figure 1. MET receptor structure. MRS (MET related sequence).

HGF-MET signaling also takes part in liver, heart and kidney regeneration (5-7). In transformed tissue, activation of MET triggers numerous biological responses leading to tumor growth and its metastasis. It promotes cancer cells dissociation, migration into circulatory system, and finally it enables reaching and colonizing new niches.

3. MET ACTIVATION IN CANCER CELLS

In normal cells, HGF binding to MET results in transient receptor phosphorylation and activation of its tyrosine kinase activity, followed by stimulation of various intracellular pathways (Figure 2). In tumor cells, MET can be activated by its ligand either in an autocrine or a paracrine manner and can be also constitutively activated in HGF-independent manner, as a result of receptor overexpression, mutation, spontaneous dimerization and transactivation by other receptors including epidermal growth factor receptor (EGFR) (8).

3.1. Autocrine activation

Although HGF is predominantly produced by cells of mesenchymal origin and acts in a paracrine manner, there is a strong evidence of its autocrine regulation in some tumors. Co-expression of HGF and the MET receptor has been detected in a variety of human tumors including breast, lung, pancreatic and thyroid cancers, glioma and myeloma (9).

Jeffers *et al.* showed that non-tumorigenic mouse cell line C127 (expressing very low level of HGF and MET proteins), engineered to overexpress both HGF and MET proteins, became phenotypically transformed, highly tumorigenic and metastatic *in vivo*. Increased level of either HGF or MET alone did not result in tumorigenic switch (10).

3.2. Paracrine activation through tumor-stroma interaction

Interactions between stroma and epithelium play a crucial role in both normal development and carcinogenesis. During development, HGF is expressed predominantly by stromal cells, while MET receptor is expressed on cells of epithelial origin (11). Paracrine activation, present at physiological conditions, can become pathological in a presence of abnormal HGF production by mesenchymal cells. In turn, HGF secretion may be stimulated by a presence of tumor cells.

The influence that stromal cells exert on epithelial neoplasia have been documented in prostate, stomach, skin, oral cavity, mammary gland and colon cancers (9). Camps *et al* demonstrated that fibroblasts accelerate growth of epithelial tumors in athymic mice (12). Most carcinoma cells *in vitro* do not invade extracellular matrix such as a collagen gel. Co-cultivation with stromal fibroblasts or fibroblast-derived conditioned media potently enhances invasion of oral squamous cells carcinoma into collagen gels (13). Increased invasiveness caused by stromal cells has been reported in various types of cancer cells, including gallbladder carcinoma, pancreatic and lung cancer cells (14-16). These observations suggest that enhancement of invasive and metastatic potential of cancer cells is mediated by a stroma-derived factors. Invasion of carcinoma cells in the co-culture system is inhibited by both antibody against HGF and competitive antagonists of HGF (16,17). These results indicate that invasion of tumor cells depends on factors produced by fibroblasts and that HGF is one of stromal-derived paracrine factors that confer invasive potential in a wide variety of cancers.

Secretion of HGF is regulated by the number of factors. Tumor cells are able to produce a variety of HGF-inducers, like epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF) (16,18) or transforming growth factor-alpha (TGF-alpha) (19).

The data mentioned above suggest the existence of mutual interactions between tumor cells and stromal fibroblasts in which tumor cells secrete molecules that

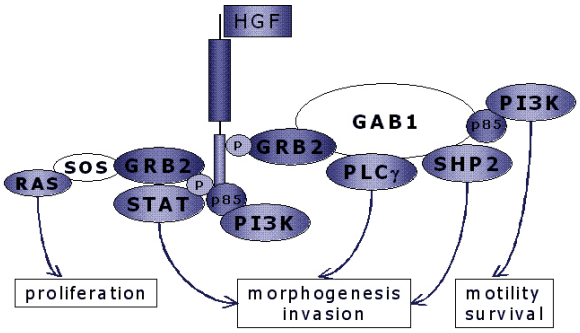

Figure 2. MET signaling network. Activation of MET results in the recruitment of adaptor proteins like Grb2 (growth-factor-receptor-bound protein 2) and Gab1 (Grb2-associated binder 1), which in turn activates SHP2 (SH2-domain containing protein tyrosine phosphatase), Ras (rat sarcoma virus oncogene), ERK/MAPK (extracellular signal-regulated kinase/mitogen-activated protein kinase), PI3K (phosphatydylinositol-3-kinase), PLC gamma (phospholipase gamma) and STAT (signal transducer and activator of transcription).

induce HGF production in fibroblasts, while fibroblasts secrete HGF which stimulates invasive growth of tumor cells.

3.3. Over-expression and mutational activation

Over-expression of the MET receptor has been noted in a wide variety of tumor cells and tissues. Increased MET receptor expression may be a result of *MET* gene amplification (20), induction by other oncogenes, such as *RAS* and *RET* (21) or transiently due to hypoxia-activated transcription (22).

Missense mutations of the *MET* gene have been reported in cancers like thyroid carcinoma, ovarian cancer and childhood hepatocellular carcinoma (23-25). Most mutations occur in a kinase domain, resulting in increase of tyrosine kinase activity. Identification of MET activating mutations found in hereditary papillary renal carcinomas provides the first direct evidence linking directly MET and human oncogenesis (26). Juxtamembrane domain mutations were observed in gastric and lung cancers (27,28). Semaphorin domain mutations lead to MET activation since this domain has been shown to bind HGF and has been demonstrated to be required for receptor dimerization and activation. This type of mutations has been found in lung cancer (28). Jeffers *et al.* showed increased levels of MET receptor kinase phosphorylation and enhanced kinase activity after introducing mutations into the *MET* gene in NIH3T3 fibroblasts. Cells expressing mutant MET gained tumorigenic potential (29).

4. CONSEQUENCES OF MET DEREGULATION

It is believed that deregulation of cell proliferation and survival, due to alteration of HGF-MET signaling may influence the tumor growth, while deregulation of motility and invasiveness may promote formation of metastasis.

4.1. Role of the HGF-MET axis in the carcinogenesis and the tumor growth

Role of HGF-MET signaling can be studied using genetically engineered mice. HGF transgenic mice develop neoplasia of both epithelial and mesenchymal origin including melanoma, rhabdomyosarcoma, mammary and olfactory carcinoma (30). Also mice generated to overexpress HGF locally, in the airway epithelium tend to develop lung cancers (31). These neoplasms express high levels of the active MET receptor, suggesting that carcinogenesis is mediated by HGF-MET autocrine loop. Mice engineered to express constitutively activated MET mutants, similarly to HGF transgenic mice, develop malignances, particularly of mammary origin (32). Overexpression of MET, obtained by lentiviral vector-mediated gene transfer, result in the conversion of primary human osteoblasts into osteosarcoma cells, displaying the transformed phenotype *in vitro* and *in vivo* (20). These data imply that deregulated form of MET appears to be equally potent factor, as the co-expression of HGF-MET. Not surprisingly, HGF-MET axis alterations, leading to autocrine activation or mutational activation of MET, can be found in a variety of tumors, both of epithelial and mesenchymal origin (9).

The HGF-MET axis controls tumor cells behavior by regulating their proliferation and survival. HGF has been shown to possess mitogenic activity. HGF-dependent cell growth control is a complex and complicated process dependent on cell context and the expression of co-receptors. For example, gastric and prostate cancer cells respond to HGF stimulation with increased proliferation (33,34), while squamous, hepatocellular carcinoma and melanoma cancer cells conversely display growth inhibition (35). HGF can protect cells from apoptosis by means of both phosphatydylinositol-3-kinase (PI3K)/AKT and mitogen activated protein kinase (MAPK) signaling (36). Moreover, HGF has been demonstrated to prevent leiomyosarcoma cells from apoptosis and HGF-induced survival can be abolished by the PI3K inhibitor LY294002, indicating that HGF inhibits cell death through the PI3K/AKT signal transduction pathway. *In vivo* inhibition of HGF and MET expression in established glioblastoma xenografts leads to induction of tumor cell death (37). MET activation alters multiple cell cycle regulators. HGF has been reported to prevent cell cycle arrest at G_1 phase induced by contact inhibition or serum withdrawal in glioma. HGF-dependant cell cycle regulation can be induced by suppression of the cyclin-dependent kinase inhibitor p27 and induction of the transcription factor C-MYC (38). On the other hand, in hepatoma cells, HGF causes G_1 phase arrest of the cell by induction of p21 expression in an ERK-dependent manner (39).

Angiogenesis is required for the growth of primary tumor and its metastasis. This process is composed of a number of events including proliferation and migration of endothelial cells and appropriate regulation of endothelial cell–cell and cell–matrix adhesion (40). HGF is one of the growth factors positively affecting tumor angiogenesis. Grant *et al.* have demonstrated HGF ability

to stimulate vascular endothelial cell migration, proliferation and organization into capillary-like tubes (41). HGF-dependant stimulation of angiogenesis has been reported for instance in papillary carcinoma or prostate cancer cells (42,43). Human breast cancer cell lines, stably transfected with *HGF* gene, exhibited more extensive tumor angiogenesis (44). HGF can act as a paracrinne factor stimulating the expression of proangiogenic cytokines like vascular endothelial growth factor (VEGF) or interleukine-8 (IL-8) (45) and downregulating angiogenesis inhibitors like thrombospondin-1 (46). HGF can also increase angiogenesis independently of VEGF, possibly through the direct activation of the AKT and ERKs in endothelial cells (47).

4.2. Role of the HGF-MET axis in metastasis

Invasion of tumor cells is a sequence of cellular events, including disruption of cell-cell adhesion and cell-matrix association at a primary site, proteolytic breakdown of the extracellular matrix, intravasation, travel and survival in the circulation, adhesion to endothelium followed by extravasation and forming a secondary site with generation of neovasculature. HGF-MET signaling affects all these processes and exhibits profound effects on the invasive behavior of a wide variety of tumor cells.

4.2.1. HGF stimulates dissociation of cancer cells at the primary site

Cell-cell adhesion plays important role in maintaining integrity of normal tissue. In cancer, cell contacts are frequently disrupted what enables dissociation of cancer cells from a main tumor mass. E-cadherin is a key cell–cell adhesion molecule in epithelial cells. It forms strong adhesive junctions between cells. Cadherins function is modulated by intracellular proteins, mainly catenins, which link the E-cadherin to the cytoskeleton (48). Activation of the MET receptor results in phosphorylation of the E-cadherin and cadherin-associated proteins, their ubiquitylation and subsequent degradation (49). E-cadherine loss disrupts adhesive junctions leading to detachment of malignant cells from a tumor mass (50).

4.2.2. HGF mediates matrix degradation and invasion

The basement membrane and extracellular matrix (ECM) is the first barrier that tumor cells encounter during their metastatic spread. Tumor cells adhere to the ECM via the integrin receptors forming complexes called focal adhesion. Integrin-mediated attachment of cells, transduces signals through focal adhesion kinase (FAK) resulting in rearrangement and retraction of cytoskeletal networks in migrating cells. HGF was shown to induce phosphorylation of FAK, which further promotes cancer cells motility (51-53). Lai *et al.* showed that MDCK cells expressing mutant FAK have no HGF-induced motility (53). Paxillin, another component of focal adhesion complexes, serves as a mechanical link between integrins and cytoskeleton. HGF was found to phosphorylate paxillin and enhanced its localization to focal adhesion complexes (52). Finally, HGF increases alpha2 and alpha3 integrin expression (51,53).

Following the adhesion of tumor cells to ECM components, they must degrade and invade through this structure. These events are facilitated by a number of secreted proteolytic enzymes. HGF induces production of various proteases such the urokinase-type plasminogen activator (uPA)-dependent proteolytic network (54), matrix metalloproteinases (MMPs) and metalloproteinases tissue inhibitors (TIMPs) (55).

4.2.3. HGF stimulates interaction of cancer cells with blood vessels, extravasation and homing.

For successful metastasis, cells must bind endothelium at a distant site and finally extravasate through it. Tumor cells capture and binding to endothelial surface is mediated by serial cell–cell adhesion mechanisms, that results in changes in the endothelium, such as an increase in the motility of endothelial cells, a temporary reduction of interaction between endothelial cells and subsequent exposure of the underneath ECM structure to allow tumor cells penetration (56).

HGF enhances transendothelial migration of cancer cells by modulating expression of adhesion molecules both on endothelial and cancer cells. CD44 facilitates initial capture of cancer cells passing over endothelium and enables interactions of other adhesion molecules. It has been demonstrated, that HGF increases adhesion of tumor cells to endothelium by increasing endothelial expression of CD44 (57) and in parallel up-regulate CD44 expression in breast cancer cells (58). HGF also promotes cell adhesion by increasing the avidity of integrins for their specific ligands (59) or simply enhancing their expression (51,60).

5. STRATEGIES AVAILABLE TO INHIBIT HGF-MET SIGNALING

Inhibitors blocking HGF-MET signaling may have therapeutic potential for the treatment of cancers in which MET activity enhances their growth and contributes to the invasive/metastatic phenotype. A number of such inhibitors have been identified. Among strategies employed to achieve HGF-MET pathway blockade, following approaches can be distinguished: (1) inhibition of HGF-MET association, (2) prevention of effective MET dimerization, (3) inhibition of MET kinase activity and (4) inhibition of MET or HGF expression (Figure 3).

5.1. Inhibition of HGF-MET association

First attempts to interfere HGF-MET signaling were focused on preventing HGF binding to the MET receptor through the use of HGF antagonists and neutralizers.

Full-length HGF is a 90 kDa protein composed of an amino-terminal domain, four consecutive kringle domains and a carboxy-terminal protease-like domain. NK1 (composed of amino-terminal hairpin domain and the first kringle domain) and NK2 (composed of amino-terminal hairpin domain and two kringle domains) are naturally occurring HGF antagonists, able to inhibit HGF-induced mitogenesis and matrix degradation (61). Concomitantly, NK1 and NK2 retain partial agonistic activity resulting in motility stimulation. NK1 and NK2

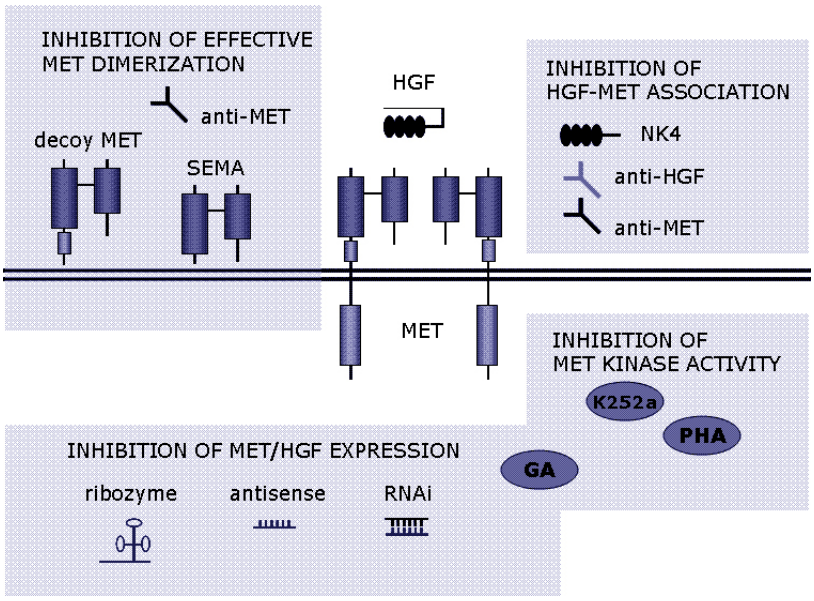

Figure 3. Strategies to target HGF-MET signaling. Gray panels represent four major strategies available to target HGF-MET axis. SEMA (semaphorin domain), PHA (PHA665752).

action is modulated by heparin and other related glycosaminoglycans (62).

NK4 is also a truncated form of HGF and contains the N-terminal hairpin domain and four kringle domains. NK4 retains binding properties without inducing MET tyrosine phosphorylation thus acts as a complete competitive antagonist. NK4 has no biological activities even in the presence of heparin (63). NK4 treatment of a variety of cancer cell lines inhibited HGF-stimulated cell motility, migration, and invasion into matrigel. Significant growth and invasion inhibition was observed in gastric carcinoma, colorectal cancer and pancreatic carcinoma cell lines (64-66). NK4 - dependent inhibition of tumor growth and invasion have been also demonstrated in many experimental mouse models, like murine Lewis Lung carcinoma and melanoma (67,68) as well as xenograft models of human breast cancer (43), gallbladder, pancreatic and prostate carcinoma (63,66,69). NK4 acts also as an angiogenesis inhibitor, restricting endothelial cells proliferation and migration stimulated by bFGF and VEGF, as well as by HGF (63,67). NK4 treatment causes decrease in the number of blood vessels in pancreatic mouse model (66). Recently, the potential use of NK4 in the treatment of hematological malignancies has also been shown. Mice bearing multiple myeloma cells expressing high level of HGF were injected intramuscularly with adenovirus carrying NK4 cDNA, what led to significant inhibition of tumor growth and vascularization of the tumor (70).

Another approach to prevent HGF binding is development of antibodies against HGF. First attempts to use antibody-based strategies revealed that successful blockade of MET activation requires combination of at least three anti-HGF antibodies. The mixture of antibodies was demonstrated to block the tumor growth of mammary carcinoma xenografts engineered to express HGF and glioblastoma xenografts that possess an endogenous HGF/MET autocrine loop (71). Martens *et al.* generated one-armed variant of the anti-MET antibody 5D5 able to inhibit HGF binding to the MET receptor thus inducing the regression of intracerebral glioblastoma xenograft growth (72).

5.2. Impairing the MET receptor dimerization

Overexpression of the MET receptor may lead to ligand - independent receptor dimerization and activation. Thus, inhibition of a receptor cross-linking seems to be a potential therapeutic target. MET dimerization blockade can be achieved with soluble form of MET (73) or even with MET semaphorin domain alone (74).

Michieli *et al.* provided evidence that *in vivo* expression of a decoy MET receptor inhibits tumor cell proliferation and survival in a variety of human xenografts, impairs tumor angiogenesis and suppresses the formation of spontaneous metastases without affecting MET housekeeping physiological functions in the adult animal. Moreover, the soluble chimeric form of MET was also shown to retain full capacity to bind HGF and therefore neutralize HGF activity (73).

Semaphorin domain is necessary for both MET receptor cross-linking and ligand binding. Kong-Beltran *et al.* reported that recombinant soluble semaphorin domain is able to inhibit HGF dependent and independent MET phosphorylation (74).

5.3. Inhibition of the MET kinase activity

Many efforts are ongoing to develop low-molecular-weight inhibitors of MET, that would inhibit MET catalytic activity or the interaction between MET and its downstream signaling molecules. The inhibition of the MET kinase activity can be achieved through agents like

geldanamycins, K252a and compounds based on indolinone core.

Geldanamycins belong to a family of ansamycin antibiotics that inhibits function of heat-shock protein 90 chaperone (HSP90). At nanomolar concentrations, geldanamycins down-regulate MET protein expression and inhibit HGF-mediated cell motility and survival of rhabdomyosarcoma cell lines (Lesko *et al*, Unpublished data). Geldanamycins treatment blocks HGF-induced migration and invasion of MDCK-2 canine kidney cells (75). At fentomolar concentrations, nine-order of magnitude below their growth inhibitory concentrations these antibiotics are potent inhibitors of HGF-mediated plasmin activation in glioblastoma cell lines, human leiomyosarcoma cells (76) and MDCK-2 cells (75). This data suggests involvement of other mechanism of geldanamycins action than simple blocking of HSP90-client proteins interaction.

K252a is a natural, staurosporine-like alkaloid that acts as a potent inhibitor for receptor tyrosine kinases of the TRK family that prevents MET autophosphorylation and activation of its downstream effectors like MAPK and AKT kinases. K252a has been shown to reduce MET-driven proliferation in gastric carcinoma cells (77).

Number of compounds defined by indolinone motif, developed by Sugen, was reported to be highly specific MET kinase inhibitors. The most potent and selective molecule identified, PHA665752, was demonstrated to inhibit HGF-stimulated and constitutive MET receptor phosphorylation (78). PHA665752 was shown to inhibit oncogenic and prometastatic properties of MET, by reducing mitogenesis, motogenesis and invasion of several tumor cell lines. Similar results were obtained with NIH3T3 engineered to overexpress MET (78). Interestingly, gastric cancer cells with *MET* gene amplification display extraordinary susceptibility to PHA665752 (79). Borset and coworkers also showed high antitumor effectiveness of PHA665752 against myeloma cells (80).

5.4. Silencing of MET or HGF expression

Gene silencing can be carried out by using antisense, ribozyme or RNAi techniques. Antisense is a single stranded RNA or DNA, 15-25 bp long, that induces cleavage of complementary target mRNA sequence or the steric block of mRNA translation. The antisense oligonucleotides effectively inhibited HGF-dependant migration of gastric cancer cells (33). Stabile *et al.* constructed U6 expression plasmids containing either the sense or antisense sequences targeting the *MET* gene. Downregulation of the MET protein level resulted in growth inhibition of non-small cell lung cancer xenograft model. MET antisense decreased phosphorylation of the MET receptor and MAPK when exposed to exogenous HGF (81).

Ribozymes are naturally occurring RNA molecules that can catalyze site-specific cleavage of RNA. Synthetic ribozymes have been shown to effectively knock out *MET* mRNA in glioma cells (37), breast cancer cells (82) and prostate cancer cells (83). Abounader *et al.* employed ribozymes to target HGF and MET gene expression in glioma xenograft model demonstrating HGF and MET protein downregulation, inhibition of MET receptor activation, tumor cell migration, and anchorage-independent colony formation *in vitro*. Moreover, ribozymes were shown to decrease angiogenesis in glioblastoma xenografts (37). Breast cancer cells, transfected with ribozyme targeting the *MET* gene, exhibited reduced migration and *in vitro* invasiveness through extracellular matrix (82). Ribozyme-driven reduction in MET expression substantially reduced both tumor growth and lymph node metastasis of prostate cancer cells in orthotopic nude mouse model (83).

Another approach to downregulate MET expression is employment of RNA interference phenomenon (RNAi). RNAi is a sequence-specific, posttranscriptional, gene-silencing mechanism that is affected through double stranded RNA molecules homologous to the sequence of the target gene. MET down-regulation obtained with lentivirus expressing an anti-Met short hairpin RNA was demonstrated to reverse transformed phenotype of osteosarcoma (20) and significantly affects rhabdomyosarcoma cells proliferation and survival (84). Our own data shows that downregulation of MET expression effectively inhibits also rhabdomyosarcoma potential to metastasis and to stimulate angiogenesis (Lesko *et al*, Unpublished data). Adenoviral construct carrying small-interfering RNA triggered reduction of MET expression in mouse mammary tumor cells and MET-transformed NIH3T3 cells, as well as both human and canine prostate cancer, human sarcoma, glioblastoma and gastric cancer cells (85).

6. CONCLUSIONS

It is well established that aberrant HGF-MET signaling plays a pivotal role in pathogenesis of many types of solid tumors and some hematological malignances. Many studies demonstrated correlation between MET expression and metastasis development, indicating MET to be a prognostic factor.

HGF-MET signaling plays important role in cancer development. MET activation exerts multiple cellular responses by 1) regulating tumor cells survival, 2) spreading and 3) formation of blood vessels. Data summarized in this review indicate that HGF and its receptor are promising therapeutic targets for clinical use. Moreover, HGF-MET signaling does not seem to be strictly required for the maintenance of tissue homeostasis in the adult, thus it seems to be likely that its targeting should be without any life-threatening adverse effects.

Modern medicine offers broad range of tools feasible to repress HGF-MET signaling, like small molecule inhibitors, cleaved forms of HGF and the MET receptor, antibodies and silencing techniques. Employment of these inhibitors should result in reduction of tumor growth and in decrease of tumor invasiveness and angiogenesis.

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Abbreviations: HGF: hepatocyte growth factor; Grb2: growth-factor-receptor-bound protein 2; Gab1: Grb2-associated binder 1; SHP2: SH2-domain containing protein tyrosine phosphatase; RAS: rat sarcoma virus oncogene; ERK: extracellular signal-regulated kinase; MAPK: mitogen-activated protein kinase; PI3K: phosphatydylinositol-3-kinase; PLC gamma: phospholipase gamma; SEMA: semaphorin domain; STAT: signal transducer and activator of transcription; EGFR: epidermal growth factor receptor; EGF: epidermal growth factor; bFGF: basic fibroblast growth factor; PDGF: platelet-derived growth factor; TGF-alpha: transforming growth factor-alpha; VEGF: vascular endothelial growth factor; IL-8: interleukine-8; TSP-1: thrombospondin-1; ECM: extracellular matrix; FAK: focal adhesion kinase; MMP: metalloproteinase; TIMP: metalloproteinases tissue inhibitor; HSP90: heat shock protein 90; RNAi: RNA interference;

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