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Does hepatocyte growth factor/c-Met signal play synergetic role in lung cancer?

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Abstract

There is growing evidence that the signal pathway between hepatocyte growth factor (HGF) and its receptor c-Met plays an important role in the development of lung cancer, although the specificity of such role is to be clarified. It seems clear that the HGF/c-Met signal contributes to the metastasis of cancer cells to the lung by stimulating the hyperproduction and overactivation of cytokines and enzymes, *e.g.* HGF, vascular endothelial growth factor and matrix metalloproteases. The HGF/c-Met signal may act as the candidate responsible for the development of epidermal growth factor receptor (EGFR) kinase inhibitor resistance. Experimental evidence showed that the combination of both EGFR and c-Met inhibitors had synergetic or additive therapeutic effects on lung cancer. Although the mechanism of interaction between HGF/c-Met and transforming growth factor-a/EGFR remains unclear, the cross-talk and balance between those two signal pathways are critical and necessary in the development of new therapies for lung cancer.

Keywords: hepatocyte growth factor • c-Met • epidermal growth factor receptor • lung cancer • therapy

Introduction

Hepatocyte growth factor (HGF), located chromosome 7q21.1, is also known as interleukin (IL)32b, scatter factor, hepatopoietin A, lung fibroblast-derived mitogen or fibroblast-derived tumour cytotoxic factor, mainly from epithelial origin cells. HGF binds to its receptor c-Met, acts as a multi-functional cytokine and regulates cell growth, motility and morphogenesis by activating a tyrosine kinase signalling cascade. The extracellular domain of c-Met comprises a large seven-bladed fl-propeller (Sema domain), a small cysteine rich domain and four immunoglobulin-like domains (Ig1–Ig4), of which the c-Met Sema and cysteine rich domains bind one domain of HGF [1]. HGF is secreted as a single inactive polypeptide and belongs to the plasminogen subfamily of S1 peptidases without the detectable protease activity [2]. It is cleaved by serine proteases into a 69-kD α-chain and 34-kD β-chain and becomes an active, heterodimeric molecule with the disulfide bond between the α and β chains. The activation of the HGF/c-Met signal pathway stimulates mitogenesis, cell motility and matrix invasion. It may play a central role in angiogenesis, tumorogenesis and tissue regeneration. The present paper is to overview the potential role of the HGF/c-Met signal pathway in the development and metastasis of lung cancer, divert inhibitions of the HGF/c-Met signal, mechanisms of HGF/c-Met involvement in the metastasis by stimulating the production of vascular endothelial growth factor (VEGF) and activating the matrix metalloprotease (MMP), and possibility to be used as an independent or combining therapeutic target.

Does HGF/c-Met signal play a role in lung cancer?

HGF has multi-functional roles in physiological and pathophysiological conditions, *e.g.* catalytic activity, serine-type endopeptidase

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activity, activation of mitogen-activated protein kinase and c-Met signalling pathway, involving organ development and regulation of mesenchymal–epithelial signalling. Out these, the amplification and mutation of c-Met associated with tumorigenesis, invasion and metastasis vary among races, *e.g.* rare in Japanese patients with NSCLC, and may predict the prognosis of patients with NSCLC [3]. HGF can be also produced by cancer cells and cancer stem cells, responsible for high tumorogenic and metastatic abilities [4]. The HGF/c-Met signal pathway could be activated in autocrine fashion and allocated in the bronchoalevolar junctions of lung tumour cells [5]. HGF was found to promote the malignant development of cancer cells by enhancing invasion and metastasis. The bifunctional transcription factor protein (NK4), as a competitive antagonist for HGF, can inhibit tumour growth and lung metastasis demonstrated in mice after the systemic administration of a replication-defective adenovirus expressing NK4 [6].

The effect of NK4 treatment is highly dependent upon the deliveries of NK4 and the intratumoural adeno-associated virus-NK4 administration had the highest therapeutic response [7]. The treatment with NK4 significantly reduced the average metastatic burden, rather than the tumour size and average numbers of macroscopic lung metastases. Experimental evidence showed that HGF could facilitate the adhesion of colon cancer cells to endothelial cells in a dose-dependent manner, while NK4 and anti-HGF antibody could reduce HGF-induced interaction between two cells and phosphorylation of focal adhesion kinase, a downstream of integrin signalling [8]. Stable NK4 expression was associated with decreased number of pulmonary metastatic foci, which could be increased by HGF. This indicates that HGF/c-Met signalling is involved in the process of haematogenous pulmonary metastasis.

There was still a lack of direct evidence to show the specificity of NK4 to the lung cancer and c-Met receptor, since NK4 *d* is a non-specific antagonist against HGF. For example, Nk4 has an additional anti-angiogenic effect independent of its HGF-antagonist function. It is also questionable whether the HGF/c-Met signal plays the role in metastasis of the cancer to the lung and has the specificity in the lung cancer, since a wide variety of human malignancies exhibit sustained c-Met stimulation, overexpression, or mutation, including carcinomas of the colon, stomach, bladder, breast, ovarian, pancreas, kidney, liver, lung, head and neck, thyroid, and prostate, sarcomas, haematological malignancies, melanoma and central nervous system tumours [9, 10].

Can the HGF/c-Met signal be blocked?

A number of c-Met pathway antagonists with potential clinical applications are involved in the main approaches, including antagonism of ligand/receptor interaction, inhibition of the tyrosine kinase catalytic activity and blockade of the receptor/effector interaction [11]. The inhibition of HGF/c-Met interaction with a single monoclonal antibody could prevent tobacco carcinogen-induced high number of tumours per mouse and tumour proliferative index, low apoptosis and overexpression of phosphorylated mitogen-activated protein kinase expression in some animals [12]. However, administration of HGF monoantibody showed little or no effects on some animals whose tumours contained mutant K-ras, an alternative downstream signalling pathway with probably competitive role of HGF/c-Met pathway. Conversely, other studies to inhibit c-Met in mice and cultured cells by genetic and pharmacological approaches demonstrated that the premalignant lung lesions progressed to multifocal lung adenocarcinomas owing to somatic mutations in K-ras. In such condition, overexpression of c-Met and high concentrations of HGF could be detected in bronchoalveolar lavage fluid and prevented by the c-Met inhibitor [13]. It indicates that c-Met may play a critical role in the development of mutant K-ras-dependent lung cancer. In addition to those main approaches, there may be more inhibitory ways of HGF/c-Met signal to be considered. For example, rapid growth of cancer cells often creates insufficient supply of oxygen and nutrients in the tumour nest. Hypoxia was found to up-regulate the expression of HGF and IL-8 responsible for cancer cell metastasis in lung adenocarcinoma, probably through the activation of prostaglandin F(2α) [14]. The CCL3-CCR5 axis signal was suggested to regulate HGF expression to accelerate neovascularization and subsequent metastasis formation probably through the production of VEGF [15].

Does HGF/c-Met regulate VEGF production?

The activation of the HGF/Met signal has been shown to induce the development and angiogenesis of lung cancer, probably by stimulating the production of VEGF. The adaptor protein Shc was suggested as the proximal signalling proteins responsible for c-Met-induced VEGF expression, since c-Met failed to induce VEGF production in the Shc-deficient condition [16]. VEGF could induce Shc recruitment to the kinases using mutants of the ν/ErbB2 receptor tyrosine kinase (RTK), where the mutant-bound Shc induced VEGF production. Shc was essential for the induction of VEGF production by the c-Met/HGF RTK oncoprotein and serum-derived growth factors. It implies that Shc acts as a critical angiogenic switch for VEGF production downstream from the c-Met and ErbB2 RTKs. Experimental findings demonstrated that c-Met was involved in tumorigenesis and liver metastasis by regulating the Src activation, since the down-regulation of c-Met could reduce Src activity and activation of ERK1/2 and Akt, followed by a decreased VEGF production, tumour size and incidence, and vessel formation in tumours [17]. The inhibition of Src could reduce basal VEGF production, proliferation, migration and anchorage-independent growth, which could be rescued by HGF. Such dose-dependent inhibitory effects on Src also reduced HGF-induced migration of tumours rather than HGF-induced anchorage-independent growth.

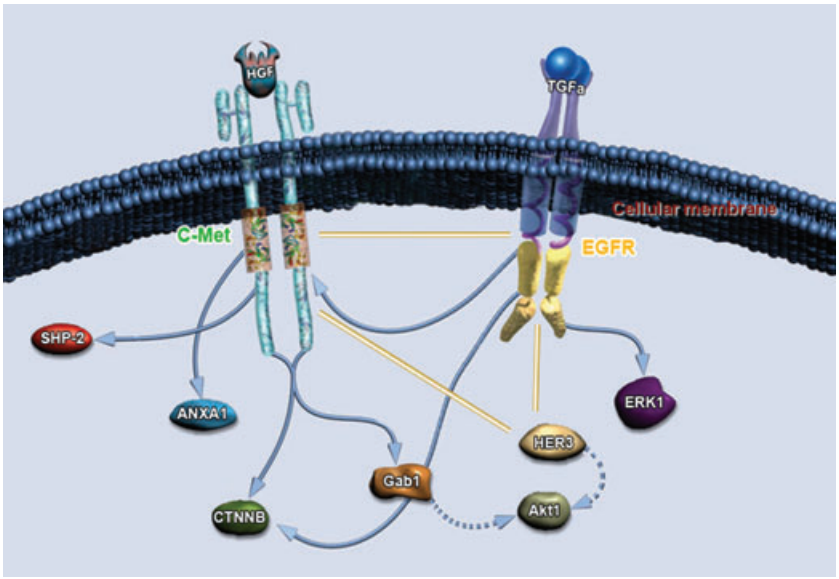

Fig. 1 TGFa/EGFR signal pathway may directly or indirectly lead to c-Met, while HGF/c-Met does not affect the phosphorylation of EGFR. TGFa/EGFR signal was proposed to activate the phosphorylation of c-Met, transcription factor ERK1, cytoskeletal reorganization factor Eps8 and adhesion factor CTNNB, while HGF/c-Met could activate the phosphorylation of endocytotic factor ANXA1, adaptor protein Gab1 and adhesion factors CTNNB and SHP2. Both TGFa/EGFR and HFG/c-Met signal pathways can directly activate CTNNB and indirectly activate the transcription factor Atk through the binding with HER3 or Gab1.

Does HGF/c-Met interact with MMPs?

HGF binds and activates c-Met through an autocrine signalling and an essential transcription factor for angiogenesis, ets-1, stimulating the matrix-degrading pathway such as the production of MMP-1 [18]. Growth factors secreted by either host or tumour cells play a major role in cell progression, by stimulating cell division and migration and modulating MMP production which are involved in the process of the invasion and metastasis. Growth factors could up-regulate the expression and activity of MMP-9 and MMP-2 in NSCLC cells where HGF and epidermal growth factor (EGF) could stimulate the conversion of MMP-9 from a latent to an active form [19]. Intrapulmonary levels of MMP-9 and HGF were found simultaneously higher during cancer metastasis to the lung [4], although the mechanism by which HGF modulates the activity of MMPs remains unclear. It is possible that mobilized cancer to the lung has higher expression of HGF and c-Met as a signal axis to increase the secretion of MMP-9 and the expression of membrane type 1-MMP and facilitate cell migration like granulocyte colony-stimulating factor induced mobilization of haematopoietic stem/progenitor cells [20]. It is also possible that HGF induces the production and activity of MMP-2, accompanied with transforming growth factor (TGF)β, fibronectin and urokinase type PA involved in junction dynamics, regulating the tight junctions by altering the synthesis of occludins and creating the proper microenvironment for tumour cell metastasis within the lung tissue like Leydig cells [21, 22]. Recent evidence demonstrated that HGF/c-Met activation could deregulate cadherin-based cell-cell adhesions, decrease the expression of cytokeratins and increase activity of MMP-2 during tumorigenesis and metastasis in premalignant and malignant (metastatic) cells [23]. Such HGF/c-Met axis activation could be balanced by the auto-secretion of an approximately 55 kD HGF fragment which was produced during the carcinoma progression and had a negatively regulatory effect on HGF signalling. Another possibility is that other factors like TGF-β_1 may up-regulate c-Met expression and activity and HGF production in the lung, resulting in increased activities of MMP-2 and MMP-9 through focal adhesion kinase phosphorylation, like in lung fibrosis [24]. Further studies on the mechanisms of constitutive activation of c-Met in lung adenocarcinoma cells demonstrated that c-Met amplification may play a more critical role than mutations in the Sema domain or any part of the cytoplasmic domain of c-Met [25]. The constitutive activation of c-Met could be associated with c-Met overexpression with or without gene amplification in the largely ligand-independent and cell-matrix adhesion-dependent pattern.

Does HGF/c-Met play a synergetic role?

The c-Met and epidermal growth factor receptor (EGFR) are potential targets of combination therapy for the cancer due to a wide expression on cancer cells during the development and progression of cancer. EGFR inhibitor has been used as a target therapy for NSCLC, of which about 80% highly expressed c-Met [8]. Co-immunoprecipitates of c-Met and EGFR were seen in protein extracts from tumour cells rather than normal cells [26]. It found that autocrine TGFa-activated EGFR caused phosphorylation of c-Met. Cross-talk between the TGFa/EGFR and the HGF/c-Met pathways might induce mitogenic or motogenic signal amplification and cell growth in the unidirectional way (Fig. 1). In the interaction between those two signalling pathways c-Met activation may initiate the transcription-dependent EGFR activation to carry out HGF-induced cell proliferation and motility [27], which was

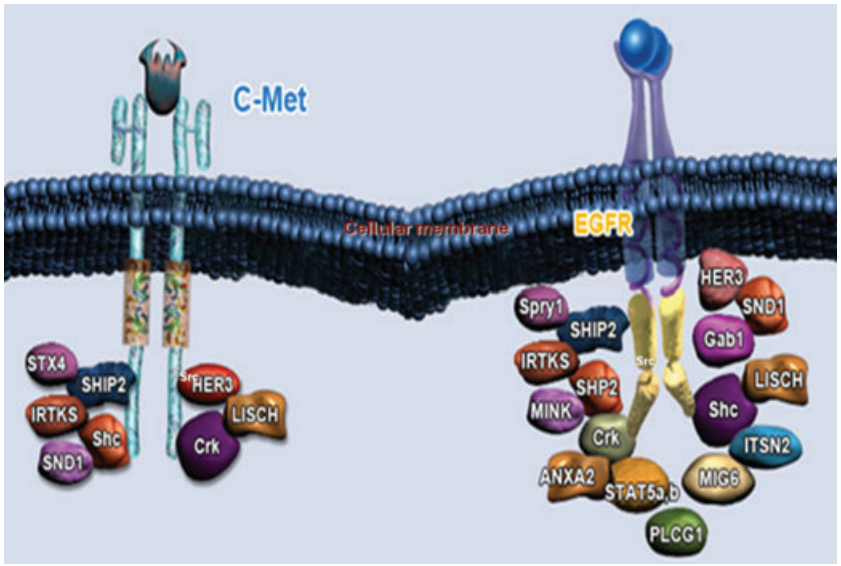

Fig. 2 The number of direct binding and indirect interaction factors of EGFR is more than c-Met in the cross-talk between TGFa/EGFR and HGF/c-Met signal pathways. There are about five to six more direct binding proteins with EGFR, *e.g.* adhesion protein SHP2, transcription factors STAT5 and 6, proliferation factor PLCG1, adaptor factor MIG6 and Gab1.

proposed to be EGFR dependent and/or through amphiregulin and heparin-binding EGF-like growth factor [28, 29]. The mechanism by which HGF induced migration of human lung cancer cells was proposed to be that Akt phosphorylation of HGF signalling inhibited the activity of phosphoinositide 3-kinase (PI3K), without affecting phosphorylation of Met and ERK [30]. Furthermore, it was demonstrated that HGF could induce EGFR inhibitor resistance of lung adenocarcinoma cells with EGFR-activating mutations by restoring the PI3K/Akt signalling pathway *via* phosphorylation of c-Met [31]. The inhibition of c-Met by siRNA rather than EGFR or ErbB3 could reverse HGF-induced EGFR inhibitor resistance and phosphorylation of Akt. In lung cancer patients with intrinsic or acquired resistance to EGFR inhibitor, the immunoreactivity for HGF became stronger in cancer cells harbouring EGFR-activating mutations but no T790M mutation or MET amplification, a novel mechanism of EGFR inhibitor resistance and a considerable strategy for more successful treatment with EGFR inhibitors.

However, the role of TGFa/EGFR-induced secondary phosphorylation of c-Met in the EGFR-dependent tumour growth remains questionable, since only a very small fraction of c-Met is phosphorylated by TGFa [26]. Recently, Gao *et al.* applied the global phosphoproteomic method to identify phosphotyrosine signalling downstream of EGFR and c-Met [32]. Amplified c-Met drives the activity of EGFR family members and mutated and amplified EGFR can also drive c-Met activity. When comparing the signalling networks in EGFR-dependent and c-Met-dependent cells, about 50 proteins were considered as the key factors to participate in pathways and mediate the response to drugs [32]. TGFa/EGFR signal was proposed to activate the phophorylation of c-Met, transcription factor ERK1, cytoskeletal reorganization factor Eps8 and adhesion factor CTNNB, while HGF/c-Met could activate the phosphorylation of endocytotic factor ANXA1, adaptor protein Gab1 as well as adhesion factors CTNNB and SHP2. Both TGFa/EGFR and HGF/c-Met signal pathways can directly activate CTNNB and indirectly activate the transcription factor Atk through the binding with HER3 or Gab1 (Fig. 1). It was proposed that c-Met might activate the EGFR agonist TGF through tumour suppressor phosphatase and tensin homolog [33].

In the cross-talk between TGFa/EGFR and HGF/c-Met signal pathways, the TGFa/EGFR signal pathway seems to play more dominate role and gain more scientific attention, most likely because the number of direct binding and indirect interaction factors of EGFR is more than c-Met [33]. There are about five to six more direct binding proteins with EGFR, *e.g.* adhesion protein SHP2, transcription factors STAT5 and 6, proliferation factor PLCG1, adaptor factor MIG6 and Gab1, as shown in Fig. 2. However, results from the study on the signalling networks between oncogenic EGFR and c-Met indicate that HGF/c-Met might have more indirect interaction with EGFR. NSCLC cell lines with the expression of both c-Met and EGFR (*e.g.* A549, H1838, H2170, SW900, SW1573, H358, SKLU-1 and H1993) had different sensibilities and responses to their ligands and inhibitors, associated with combining doses, rationales and durations [34]. For example, EGF and HGF at 100 ng/ml showed a synergistic effect on A549, H1838 and SKMES cell proliferation at 48–72 hrs. HGF (40 ng/ml) and EGF (5 ng/ml) induced synergistic phosphorylation of c-Met (Tyr 1003/1230/1234/1235). EGF and HGF at 100 ng/ml for 2 hrs had an additive effect on he induction of cell motility (especially membrane ruffling) in H1993 cells. The combination of c-Met tyrosine kinase inhibitor SU11274 (2 mM) and EGFR tyrosine kinase inhibitors Tyrphostin AG1478 (0.5 mM) had a synergistic effect on inhibition of cell proliferation (65%), while EGFR inhibitor (gefitinib, Iressa) and c-Met inhibitor (SU11274) had a synergistic effect on apoptosis. Those data indicate that there may be other factors contributing to the sensitivity and activation of c-Met and EGFR in addition to the cross-talking between EGFR and c-Met.

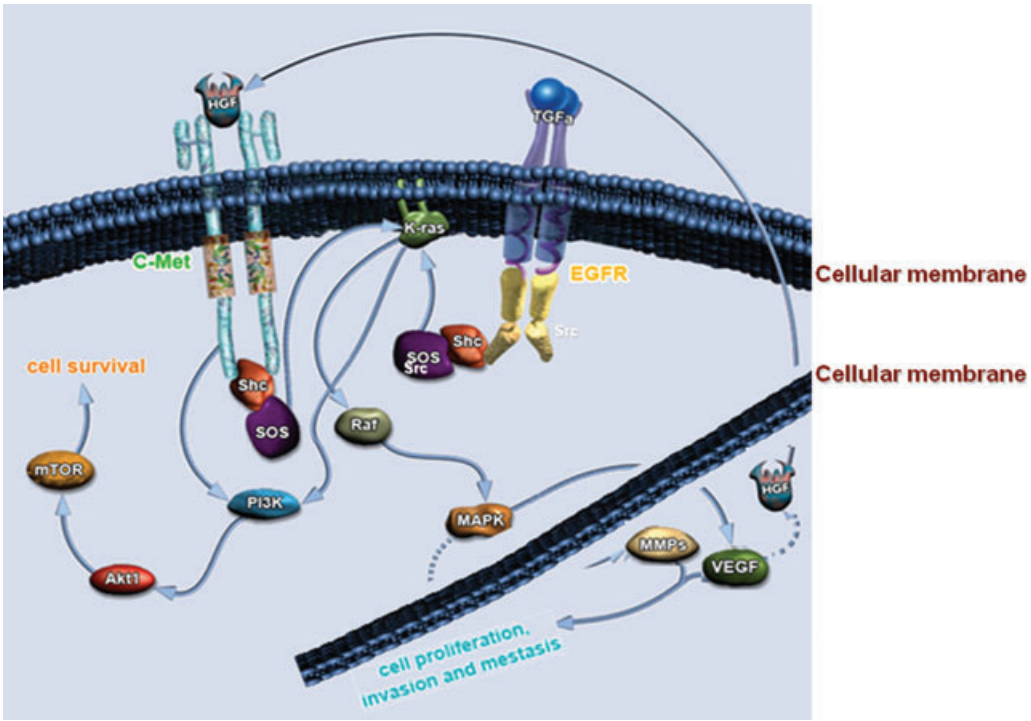

Fig. 3 The potential mechanism of the HGF/c-Met signal pathway hallmarks in lung cancer. Both HGF and TGFa can activate PI3K and MARK signal pathways directly and indirectly through the K-ras, leading to the production of HGF, VEGF and MMPs and regulating cell proliferation, invasion and metastasis in NSCLC.

Does HGF/c-Met contribute to EGRFI therapeutic sensitivity?

HGF/c-Met is considered to be one of the candidates responsible for the development of EGFR inhibitor resistance in the therapy for NSCLC, since both are a family of oncogenes and regulate important cellular processes. Amplification of c-Met caused gefitinib resistance by driving ERBB3 (HER3)-dependent activation of PI3K in NSCLC, a pathway specific to EGFR/ERBB family receptors [35]. c-MET signalling may play a key role in lung cancer oncogenic signalling and interface with EGFR, which may be an alternative co-therapy for EGFRI resistance NSCLC (Fig. 3). c-Met amplification occurred independently of EGFRT790M mutations, indicating that c-Met may be a clinically relevant therapeutic target for some patients with acquired resistance to EGFR inhibitors [36]. Experimental results demonstrated that both Met and EGFR were expressed in the EGFRI-resistant lung cancer cell line H1975 (L858R/T790M-mutant EGFR) and c-Met signalling had EGFR-inhibitor-resistant role in lung cancer [37]. The HGF/c-Met signal path was functional and activated in EGFR-inhibitor-resistant cells with the oncogenic mutant EGFR (L858R/T790M) signal axis. It was demonstrated that dual treatment using a c-Met inhibitor plus a reversible or irreversible EGFR kinase inhibitor had more significant inhibitory effects, as an alternative strategy to circumvent T790M-EGFR-mediated resistance in lung cancer.

The clinical study showed the most of patients (7/9) with EGFR-inhibitor-resistant tumours had a secondary T790M mutation, while the expression of HGF and c-Met was only observed in EGFR-inhibitor-resistant tumours when T790M mutation existed [38]. It seems that the HGF/c-Met signal may play a partial or assistant role in the development of EGFR-inhibitor-resistance. There is also possibility that c-Met phosphorylation may play more important role than its overexpression. c-Met may be indirectly involved *e.g.* by the binding of the invasion protein of Listeria monocytogenes, a gram-positive, facultative intracellular human pathogen [39]. The c-Met can be activated when the capped leucine-rich repeat domain of the invasion protein interacts with the high affinity Met-binding site, followed by an additional activation of inter-repeat region, an immunoglobulin (Ig) like moiety. Without the third party, c-Met is still inactivated although the high affinity binding site exists. Overexpression of c-Met was not sufficient to cause such activation [40].

HGF was found to suppress apoptosis-inducing factor expression and increase resistance of non-specific chemotherapy drugs for NSCLC, *e.g.* cisplatin, through c-met and its downstream effector, focal adhesion kinase [41]. Flavonoids (apigenin) could inhibit HGF-induced cancer cell motility, scattering, migration and invasion in a dose-dependent manner through down-regulation of Akt phosphorylation rather than c-Met, ERK and JNK phosphorylation [42]. Such non-specific compounds inhibited the HGF-induced clustering and function of β_4 integrin at actin-rich adhesive site and lamellipodia, including cell-matrix adhesion and cell-endothelial cells adhesion through PI3K-dependent manner.

In conclusion, there is growing evidence that the HGF/c-Met signal play an important role in the development of NSCLC,

although the specificity of such role needs to be clarified. It seems clear that the HGF/c-Met signal contributes to the metastasis of cancer cells to the lung by stimulating the hyperproduction and overactivation of cytokines and enzymes, *e.g.* HGF, VEGF and MMPs. Although the mechanism of interaction between HGF/c-Met and TGFa/EGFR remains unclear, the cross-talk and balance between those two signal pathways are critical and necessary in the development of new therapies for NSCLC. There are great needs to investigate the combining strategy of c-Met and EGFR inhibitors, therapeutic efficacy and rational of their combination and optimal delivery of drugs. It is to be clarified whether c-Met inhibitors can be applied as the backup if EGFR inhibitors fail or both should be simultaneously used as a personalized medicine.

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