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REVIEW ARTICLE

Research progress of the role of HGF/c-Met in the proliferation, invasion, angiogenesis and metastasis of cancer

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Abstract

The HGF/c-Met pathway plays an important role in the proliferation, invasion, angiogenesis, and metastasis of tumors. With the successful development of small molecule c-Met kinase inhibitors, this signal pathway has become the focus of oncology research. In this review, we discuss the basic mechanism, targeted therapy, and early results of clinical trials of the HGF/c-Met pathway.

Key words: HGF/c-Met pathway; targeted therapy; drug resistance; clinical trial

Hepatocyte growth factor/scatter factor (HGF/SF) and its receptor (c-Met) were discovered in the mid-1980s. Met protein was first identified in human osteogenic sarcoma and its coding gene was later found to encode the receptor tyrosine kinase [1]. In 1991, basic experiments identified HGF/SF as the c-Met ligand, which was confirmed by a gene knock-out mouse model [2]. An analysis of this signaling pathway highlighted the essential physiological roles of proteins encoded by these genes in survival, growth, and migration of several cell types and tissues.

A striking feature of the HGF/c-Met signaling pathway is the diversity of cellular responses that follow c-Met activation, which activates downstream targets of c-Met and its associated docking proteins, such as growth factor receptor-bound protein 2 (GRB2) and associated binding protein 1 (GAB1) [3]. Crosstalk also exists between this pathway and other signaling systems, and numerous discoveries have brought into focus the role of the HGF/c-Met pathway in cancer. This review mainly focuses on the roles of the HGF/c-Met pathway in cancer and the progress in the development of inhibitors for targeted therapies.

The structure and basic mechanisms of the HGF/c-Met pathway

HGF is synthesized as a single chain and is composed of six domains: an N-terminal domain, four copies of the kringle domain, and a C-terminal serine proteinase homology (SPH) domain. However, c-Met is a heterodimer, which is formed by an amino-terminal α-chain and a larger β-chain. The c-Met ectodomain consists of a large N-terminal Sema domain, which adopts a seven bladed β-propeller fold and a stalk structure consisting of four immunoglobulin-like domains [4].

The c-Met protein is a transmembrane receptor tyrosine kinase. HGF-induced c-Met dimerization activates the tyrosine kinase by phosphorylation of tyrosine residues (Tyr1230, Tyr1234, and Tyr1235) in the kinase domain, which leads to autophosphorylation of the carboxy-terminal bidentate substrate-binding site (Tyr1349 and Tyr1356) of c-Met. Then, several cytoplasmic effector proteins, including phospholipase C (PLC), SRC, and GAB1 are directly recruited to this site, and these proteins are also frequently phosphorylated on tyrosine residues. Phosphorylated GAB1 bound to c-Met at the plasma

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membrane can further attract other proteins such as SRC, PI3K, CRK-like protein, and others that together activate various downstream signaling cascades [5]. C-Met signaling, which engages in crosstalk with the RAS-MAPK and PI3K-AKT pathways, affects gene expression and cell cycle progression.

HGF/c-Met pathway in tumors

Receptor tyrosine kinases are a subclass of cell surface growth factor receptors with an intrinsic ligand-controlled tyrosine kinase activity that play a crucial role in oncogenesis [6]. As a member of the receptor tyrosine kinase family, c-Met can be activated by way of overexpression, activating point mutations and others in many tumor types, without the need for ligand binding [7]. Furthermore, activating mutations of c-Met have been found in numerous cancers including lung, gastric, liver, kidney, and ovarian cancer [8]. Many studies have also shown the relationship between c-Met amplification and expression with poor clinical outcome in patients with cancer [9–10]. Thus, c-Met may provide a good target for treatment to delay or prevent cancer progression.

Crosstalk between c-Met and other signaling pathways

C-Met interacts with other tyrosine kinase receptors such as RON, epidermal growth factor receptor (EGFR), and ERBB2 as well as other membrane receptors, including integrin α6, β4, the adhesive molecule CD44, and FAS.

RON, also known as stem cell derived tyrosine kinase in mice, displays 25% homology with c-Met in the extracellular region and 63% homology in the tyrosine kinase domain [11]. Interestingly, the ligand that binds to RON is an HGF-like protein that shares 45% amino acid identity with HGF. RON activity is characterized by the production of distinct variants through alternative splicing, protein truncation, or alternative transcription, which have different morphological features and oncogenic potential. HGF-activated c-Met results in RON cross-phosphorylation and vice versa. Therefore, activating one receptor of RON or c-Met can lead to the activation of the downstream targets within the two signaling pathways.

C-Met interacts with EGFR in several ways. C-Met is amplified in lung cancer cell lines treated with EGFR-TKI, which leads to activation of EGFR downstream pathways such as PI3K-AKT, and acquired resistance of EGFR-TKI [12]. C-Met amplification is common in gastric cancer cells, and selective blockage of c-Met-related molecular events in such cells stops the crosstalk activation of EGFR and ERBB3 [13]. Her-2, also known as ERBB2, has never been reported to have a direct physical interaction with the c-Met receptor. However, the synergistic activity of the two receptors enhances the malignant phenotype in cancers where Her-2 is overexpressed [14]. Additionally, high expression of c-Met and HGF are associated with an increased risk of trastuzumab-based therapy failure in Her-2-positive metastatic breast cancer [15].

Crosstalk between c-Met and developmental signaling pathways, such as WNT/β-catenin and TGFβ/bone morphogenetic protein (BMP), has also been demonstrated. The high frequency of WNT pathway mutations in many different cancers demonstrates that the WNT/β-catenin pathway can cause cancer [16]. C-Met is a direct transcriptional target of WNT/β-catenin in colon cancer cell lines and other tissues. Unfortunately, WNT/β-catenin signaling is a key downstream mediator of c-Met signaling in glioblastoma stem cells [17]. There may be additional tumor types in which the WNT and c-Met pathways cooperate to maintain a cancer stem cell compartment. The relationship between c-Met and TGFβ/-BMP is more complex and needs further research.

Targeting HGF/c-Met in cancer

Different strategies have been developed to inhibit the HGF/c-Met pathway. These therapies target the different steps of c-Met signaling activation: the interaction between c-Met and its ligand HGF, receptor transphosphorylation and activation, kinase activity, and phosphorylation of the signal transducer docking site as well as others.

The HGF inhibitors include biological antagonists and monoclonal antibodies. NK1, NK2, and NK4 are the three most important antagonists. NK1 and NK2, which contain the N-terminal domain and two natural splice variants of HGF, inhibit HGF-induced epithelial mitogenesis and morphogenesis. NK4, a synthetic truncated form of HGF, inhibits a number of c-Met-dependent responses and also acts as an angiogenesis inhibitor [18]. Neutralizing MAbs against human HGF, such as L2G7, AMG102, and SCH900105, each potently suppressed the growth of tumor xenografts in mice, but they require more clinical trials to determine their efficacy and safety.

Several c-Met antibodies with antagonistic activity are now available. Onartuzumab is a monovalent antibody that displays potent antagonistic activity by binding the Sema domain of c-Met and thus preventing the receptor from combining with HGF [19]. Other c-Met antibodies, such as CE-355621 (Pfizer), PHA-665752 (Pfizer), K252a (Fermentek Biotechnology), and OA-5D5 (Genetech), are currently being investigated in preclinical studies [20]. Impressive numbers of c-Met kinase inhibitors have been developed over the past decade. Crizotinib is a selective oral small molecule inhibitor of the ALK (anaplastic lymphoma kinase) tyrosine kinase receptor. Apart from

this, crizotinib is also a tyrosine kinase inhibitor of c-Met and ROS1 [21]. Tivantinib is a unique agent that is the first non-ATP competitive small cell compound that targets c-Met in a highly selective fashion. Clinical in vivo studies have demonstrated the agent's antineoplastic action against various cancers, such as colorectal cancer, gastric cancer, and breast cancer [19]. Cabozantinib is a potent oral inhibitor that blocks signal transmission through c-Met, VEGFR2, and RET, and has antiangiogenic and antitumorigenic properties with potential efficacy for the treatment of several cancers [22]. Foretinib is also an oral multikinase inhibitor that exhibits activity against c-Met and a number of other tyrosine kinase receptors engaged in angiogenesis and in the progression of neoplastic disease [23]. As the HGF/c-Met pathway becomes a therapeutic target for preventing invasion and metastasis, which arehallmarks of cancer [24], a series of small molecule inhibitors targeting the c-Met receptor are being invented for clinical use.

Early results of clinical trials

The vast majority of the clinical trials that aim to define the efficacy of HGF/c-Met therapeutics are currently in progress, and initial results from several studies have been made available. AMG 102 (Rilotumumab) is a fully humanized, monoclonal antibody that selectively binds to HGF. Its tolerance and toxicity were evaluated in combination with angiogenesis inhibitors in adult patients with advanced solid tumors. In two phase II clinical trials, Rilotumumab was found to extend PFS and OS in gastric cancer, and phase III clinical trials are underway [25–26]. Onartuzumab, a recombinant, humanized, monoclonal antibody that binds to c-Met, improved PFS and OS in the c-Met-positive patients with advanced non-small cell lung cancer in a randomized phase II trial [27]. However, in March 2014, the company Genentech announced the termination of the study due to the lack of clinical efficacy of onartuzumab in the primary analysis of the results obtained after the recruitment of 499 patients [28].

In the field of c-Met inhibitors, there are many new drugs undergoing clinical trials. In the ongoing clinical trial, the efficacy and safety of crizotinib was assessed in c-Met-amplified non-small cell lung cancer. At data cutoff, four partial remissions were observed (95% CI: 10.65), and the median duration of response was 35 weeks (95% CI: 16.112) [29]. A phase III study of erlotinib ± tivantinib as the first-line of treatment for nonsquamous NSCLC patients was terminated very early by an independent data monitoring committee due to the inability to achieve the assumed difference in terms of the study's primary endpoint: OS [30]. However, tivantinib is under clinical trial for the treatment of other cancers. The efficacy and safety of cabozantinib in monotherapy for solid tumors were initially assessed in a multicenter phase I clinical study with dose escalation [31]. Then, in a phase II randomized discontinuation trial, cabozantinib was shown to have clinical activity in men with castration-resistant prostate cancer, including reduction of soft tissue lesions, improvement in PFS, resolution of bone scans, and reductions in bone turnover markers, pain, and narcotic use [32]. Cabozantinib also achieved a statistically significant improvement in PFS in patients with progressive metastatic medullary thyroid cancer in a phase III trial [33].

Mechanism of resistance to HGF/c-Met pathway

Therapies targeting receptor tyrosine kinases have shown efficacy in molecularly defined subsets of cancers. Unfortunately, cancers invariably develop resistance, and overcoming or preventing resistance will ultimately be the key to unleashing their full therapeutic potential. Similar to the acquired resistance to EGFR targeted therapies, there are two mechanisms of resistance that arose simultaneously [34]. One cause of resistance is a mutation in the c-Met activation loop (Y1230) and the other is activation of the EGFR pathway due to increased expression of transforming growth factor-α.

Summary

The availability of a wealth of HGF/c-Met inhibitors with a range of potencies and specificities has provided a strong basis for assessing the therapeutic value of HGF/c-Met inhibition in human cancer. Initial results from clinical studies have demonstrated the therapeutic benefits of the inhibitors in patients with a variety of advanced or metastatic tumors, including NSCLC, breast, prostate, liver, and renal cancer. Although many questions remain unanswered, preclinical and early clinical results obtained using anti-HGF/c-Met drugs suggest that c-Met targeting represents a valuable opportunity, and that combined therapies with drugs directed against c-Met and other tyrosine kinase receptors can probably help improve the outcome of cancer patients in the era of precision medicine.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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