MINIREVIEW

HGF/SF-Met signaling in tumor progression

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ABSTRACT

Tumor progression is a multi-step process that requires a sequential selection of specific malignant phenotypes. Met activation may induce different phenotypes depending on tumor stage: inducing proliferation and angiogenesis in primary tumors, stimulating motility to form micrometastases, and regaining the proliferation phenotype to form overt metastases. To study how HGF/SF-induced proliferative phenotypes switch to the invasive phenotype is important for understanding the mechanism of tumor progression and will provide an attractive target for cancer intervention and therapy.

Keywords: HGF/SF-Met, signaling, tumor progression.

INTRODUCTION

The *Met* gene encodes the tyrosine kinase receptor for hepatocyte growth factor (HGF)/scatter factor (SF)[1]. The exposure of Met-expressing cells to HGF/SF can elicit a variety of cellular responses including proliferation, migration, invasion, and branching morphogenesis [2]. While HGF/SF-induced cellular effects are required for many normal physiological processes, inappropriate Met activation has been implicated in most types of solid tumors, often correlating with poor prognosis (http://www.vai.org/vari/metandcancer). Since Met signaling contributes to tumor survival, growth, angiogenesis, and metastasis, it provides a potential target for cancer therapy. This review will focus on recent progress on the role of HGF/SF-Met signaling in tumor development and progression.

HGF/SF-MET SIGNALING

Met receptor consists of a 140-kDa membrane-spanning β chain and a 50-kDa extracellular α chain. The two subunits are disulphide-linked to form a 185-kDa heterodimeric complex. The β subunit contains an extracellular portion involved in ligand binding, a membrane-spanning segment, a juxtamembrane domain, a catalytic domain, and a C-terminal docking site [3]. The binding of HGF/SF to Met triggers autophosphorylation of the cytoplasmic domain of Met. The phosphorylation at two tyrosine residues in the catalytic domain, Y1234 and Y1235, is crucial for activating Met as a tyrosine kinase, while phosphorylation at Y1349 and Y1356 in the C-terminal docking site is essential for recruiting adaptor proteins [4]. Adaptor proteins contain a Src homologous2 (SH2) domain that interacts with Met receptor and a Src homologous3 (SH3) domain that binds to downstream signal molecules.

Grb2 and Ras-MAPK signaling

Grb2 adaptor protein associates with Met through the Grb2 SH2 domain, and Grb2 interacts with SOS1 through its SH3 domains. SOS1 activates Ras, which triggers ERK1/2/MAPK signaling through Ras-Raf-Mek1, 2. This signal pathway has been reported to be involved in HGF/SF-induced cell migration, invasion, and branching morphogenesis [5].

Gab1 and its down stream adaptors

Gab1 binds to Met with its unique Met-binding site [6]. Gab1 may also be recruited through Grb2. Activated Met phosphorylates Gab1 at several tyrosine residues that are required for recruiting downstream SH2-domain-containing proteins including PLC-γ, SHP2, Crk/CRKL, Gab1, and PI3K. The functions of the downstream adaptor proteins have been characterized by using Gab1 molecules with mutations at specific tyrosine residues. For example, expression of a Gab1 mutant molecule (Y307/373/407F) that is unable to bind PLC-γ completely abolished HGF/

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SF-mediated tubulogenesis [7], while a Gab1 mutant at Y673 that fails to recruit SHP2 blocks the sustained ERK1/2 activation and epithelial morphogenesis emanating from Met [8]. Both c-Crk and CRKL bind to Tyr-*X*-*X*-Pro (Y*XX*P) motifs in Gab1 and recruit C3G and DOCK180 [9]. C3G is a guanine-nucleotide exchange factor that regulates adherent junction positioning and cell adhesion by activating Rap1 [10]. DOCK180 activates Rac1, which mediates Met-induced cell spreading and migration [11]. PI3K/Akt signaling is required for HGF/SF-induced scattering and branching morphogenesis [12]. It is also the main mediator of HGF/SF-induced cell survival [13].

SHIP-1, Src, and Stat3

These proteins directly bind to a Met docking site and mediate different cellular responses. SHIP-1 is required for HGF/SF-mediated branching morphogenesis [14]. Src may be involved in HGF/SF-induced cell transformation [3]. The activation of Stat3 leads to the expression of genes required for HGF/SF-induced branching morphogenesis or anchorage-independent cell growth [15, 16].

c-Cbl and termination of c-Met signaling

c-Cbl is recruited to the Met receptor by two distinct mechanisms: direct binding to the Met juxtamembrane domain via its TKB domain, and indirect binding through Grb2 via a proline-rich domain. As a ubiquitin-protein ligase, c-Cbl targets Met for ubiquitylation and internalization to terminate Met signaling [17, 18]. In addition to the down-regulation of Met protein, Met downstream signaling pathways can be negatively regulated by the HGF/SF-responsive gene product Spry2 [19].

ACTIVATION OF HGF/SF-MET SIGNALING IN TUMORS

Met is primarily expressed in epithelial cells, while HGF/SF is produced by surrounding mesenchymal cells. This ligand/receptor-mediated cross-talk between the epithelial and stromal compartments is required for normal physiological processes and is tightly regulated [20]. Many tumors constitutively express both HGF/SF and Met to evade spatial and temporal regulatory mechanisms. The autocrine activation of Met occurs in osteosarcomas and glioblastomas, while Met activation in breast cancer, prostate cancer, and lung cancer is believed to be paracrine [2]. In tumor cells, Met also can be activated in a ligand-independent manner through Met overexpression or mutation [20]. A high level of Met has been described in many carcinomas and is required for maintaining tumor growth and survival [21]. In hepatocytes, Met directly binds to Fas and prevents Fas-induced apoptosis in an HGF/SF-independent manner [22]. Met mutations in the tyrosine kinase domain have been found in both sporadic and hereditary forms of human papillary renal carcinomas [23]. These mutations exhibit increased levels of kinase activity and tumorigenic activity in NIH3T3 cells [24] and give rise to a completely different spectrum of tumors when introduced into the mouse germline [25]. Met mutations in the juxtamembrane (JM) domain have been reported in gastric cancer and lung cancer [26, 27]. The JM domain is involved in the interaction between Met and c-Cbl. Mutation at this domain prevents down-regulation of Met and leads to extended Met signaling [28].

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