## REVIEW ARTICLE

# Hepatocyte Growth Factor Signaling Pathway as a Potential Target in Ductal Adenocarcinoma of the Pancreas

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### ABSTRACT

Hepatocyte growth factor is an important cellular signal pathway. The pathway regulates mitogenesis, morphogenesis, cell migration, invasiveness and survival. Hepatocyte growth factor acts through activation of tyrosine kinase receptor c-Met (mesenchymal epithelial transition factor) as the only known ligand. Despite the fact that hepatocyte growth factor is secreted only by mesenchymal origin cells, the targets of this multifunctional pathway are cells of mesenchymal as well as epithelial origin. Besides its physiological role recent evidences suggest that HGF/c-Met also plays a role in tumor pathophysiology. As a "scatter factor" hepatocyte growth factor stimulates cancer cell migration, invasion and subsequently promote metastases. Hepatocyte growth factor further is involved in desmoplastic reaction and consequently indorse chemo- and radiotherapy resistance. Explicitly, this pathway seems to mediate cancer cell aggressiveness and to correlate with poor prognosis and survival rate. Pancreatic Ductal Adenocarcinoma is a carcinoma with high aggressiveness and metastases rate. Latest insights show that the HGF/c-Met signal pathway might play an important role in pancreatic ductal adenocarcinoma pathophysiology. In the present review, we highlight the role of HGF/c-Met pathway in pancreatic ductal adenocarcinoma with focus on its effect on cellular pathophysiology and discuss its role as a potential therapeutic target in pancreatic ductal adenocarcinoma.

## INTRODUCTION

Hepatocyte growth factor (HGF) is a multifunctional gene. It was previously known for its role in the signaling pathway especially in hepatocytes and described as a heparin-binding polypeptide [1, 2, 3, 4]. HGF acts in hepatocytes as a potential mitogen regulator, stimulates DNA replication, controls organogenesis and organ regeneration [3, 5, 6]. The roles of HGF in liver regeneration following both drug induced liver injury and partial hepatectomy have been already demonstrated [6, 7, 8, 9, 10]. However, previous studies showed that HGF performs its numerous roles not only in hepatocytes, but also in other cell types through activating its downstream signalings and consequently stimulation of DNA synthesis [11, 12].

HGF is secreted by cells of mesenchymal origin, but acts not only in cells of mesenchymal but also epithelial origin. Its action is mediated by binding its receptor c-Met (mesenchymal epithelial transition factor). This

activation causes auto-phosphorylation of c-Met and subsequent activation of downstream signaling pathways such as mitogen-activated protein kinases (MAPKs), phosphatidylinositol-3 kinase (PI3K), signal transducer and activator of transcription (STAT), nuclear factor-kappaB (NF-κB) [1, 13, 14]. Therefore, activation of HGF/c-Met signaling activates pathways which regulate cell differentiation, proliferation, transformation, migration and apoptosis [3, 14, 15, 16, 17, 18, 19, 20, 21]. An essential role of this pathway in wound healing has been also described [22, 23, 24, 25, 26].

In addition to the productive and protective roles of the signaling pathway in fetal development, organogenesis and organ regeneration [3, 4, 18, 22, 27, 28, 29, 30], recent studies suggested an importance of HGF/c-Met signaling pathway in cancerogenesis as it correlates with poor prognosis and high metastasis rate [12, 31, 32, 33, 34]. Possible ways of action of the pleiotropic HGF/c-Met signaling pathway in tumorigenesis include activation of proliferation, cell de-differentiation and activation of epithelial mesenchymal transition [13, 35, 36, 37].

Many clinical characteristics of cancers, like metastasis rate, are meant to be dependent on the fraction of cancer stem cells (CSCs) within the tumor [38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48]. CSCs are a small population of cancer cells having ability of epithelial–mesenchymal transition (EMT), self-renewal, aggressiveness, apoptosis resistance, invasive, uncontrolled growth [37, 41, 47, 49, 50, 51, 52, 53, 54, 55, 56]. The cancer stem cells are defined by certain surface markers [57]. Recently, HGF/c-Met was also suggested as marker for CSCs [46, 58, 59, 60, 61, 62, 63, 64, 65, 66].

Interestingly, overexpression of c-Met and its ligand have been detected in PDAC and can be detected in pancreatic cancer stem cells, too [56, 67, 68, 69, 70]. Increasing number of recent studies suggested an association between high c-Met and HGF expression and stem cell features of the tumor [34, 56, 59, 70, 71, 72, 73, 74]. However its definite role in PDAC still needs to be thoroughly investigated and comprehensively described.

## HGF

The HGF, also known as "scatter factor" (SF), was initially found in the blood of hemihepatectomized rats and described in 1984 as a mitogen protein for hepatocytes [4, 14]. HGF is a cytokine belonging to the serine protease family and known as a unique ligand of c-Met cell surface marker. The gene is located on chromosome 7q21.1 in 70 kb length [75].

HGF is synthesized in mesenchymal cells as inactive single chain protein and obtains its active heterodimer form via cleaving catalysis by serine proteases in the extracellular environment [1, 13] . An active form of HGF comprises α and β chains with 69 and 34 kDa correspondingly. The heavy α chain contains five domains: N-terminal domain and four kringle domains. Kringle domains are responsible for protein-protein interaction [64]. The light β chain constitutes a serine protease homology (SPH) domain and has a catalytic feature **(Figure 1)** [75, 76]. The N-terminal domain and the first Kringle domain of HGF (NK1 section) are the essential receptor-binding fragment which regulates receptor-ligand connection [76].

## c-Met

c-Met is a pro-oncogenic protein, also called hepatocyte growth factor receptor (HGFR) or receptor tyrosine kinase (RTK). c-Met is a transmembrane tyrosine kinase which is encoded by Met gene **(Figure 2)** [75, 76]. The gene encoding c-Met is located on chromosome 7q21-31 in 120kb length [77]. c-Met is composed of a 50-kDa, totally extracellular α chain and a 140-kDa, transmembrane β chain complex with disulfide link [75]. Therefore, c-Met has large extracellular, transmembrane and cytoplasmic parts.

The extracellular part of c-Met contains three domains: semaphorin domain (SEMA); Met related sequence domain (MRS) and immunoglobulin domain (Ig). The SEMA domain constitutes of the whole α chain and the N-terminal part of the β chain. This domain controls protein-protein interaction. The SEMA domain is followed by MRS domain, which is rich with cysteine and involved in the right placing of the receptor during binding with HGF receptor. These two domains create the semaphorin homology region containing about 500 amino-acid. This fragment is found almost in all Met receptor subfamily [78]. Finally, four Ig domains conclude the extracellular c-Met [75].

The cytoplasmic part of c-Met comprises the juxtamembrane domain, tyrosine kinase domain and the C-terminal part [13, 75, 79, 80]. The former is responsible for c-Met ubiquitination [81]. Contrary, the kinase domain has the ability to catalyze. The C-terminal part is a multifunctional docking site and controls the enrollment of downstream connectors [75, 76]. As mentioned before
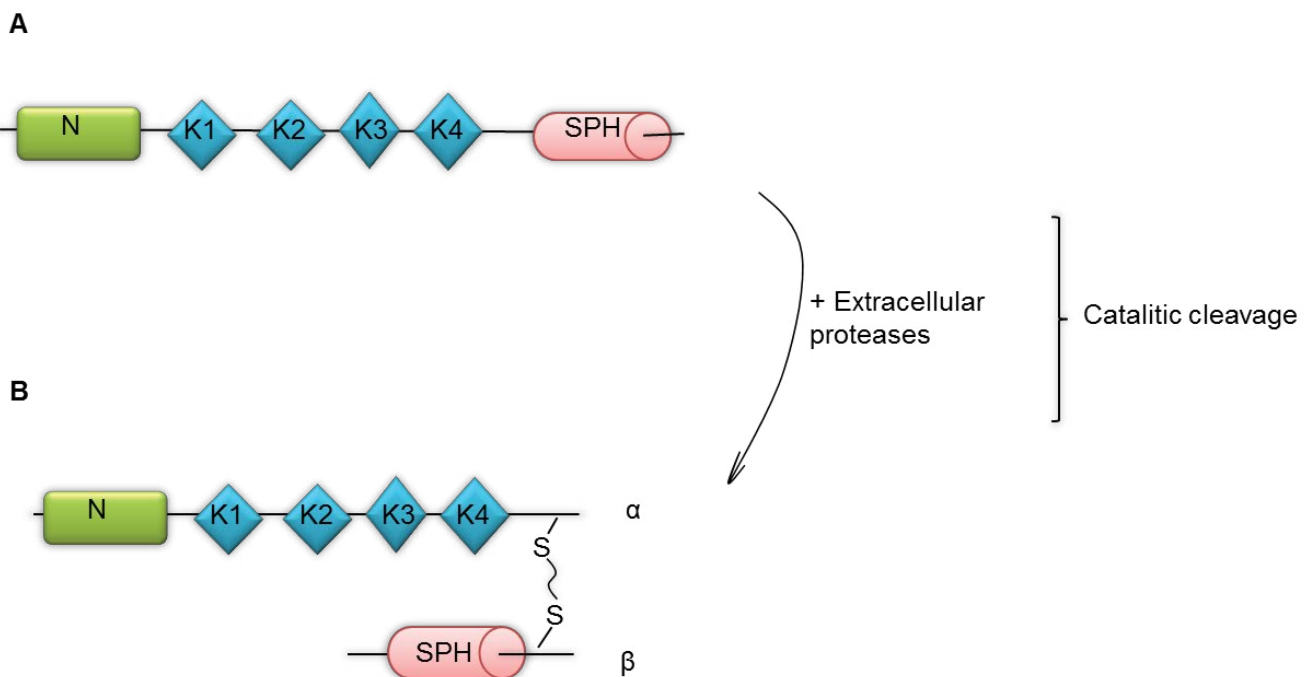


**Figure 1.** Maturation and domain structure of Hepatocyte growth factor (HGF).

**(a).** Inactive HGF; **(b).** Mature HGF.

Inactive single chain HGF is turned into its 2 chains biologically active form by cleavage process in an extracellular area. Mature HGF consists of heavy α and light β chains, 69 and 34 kDa correspondingly. Demonstrated are N-terminal and four Kringle domains – α chain; Serine protease homology (SPH) domain - β chain.
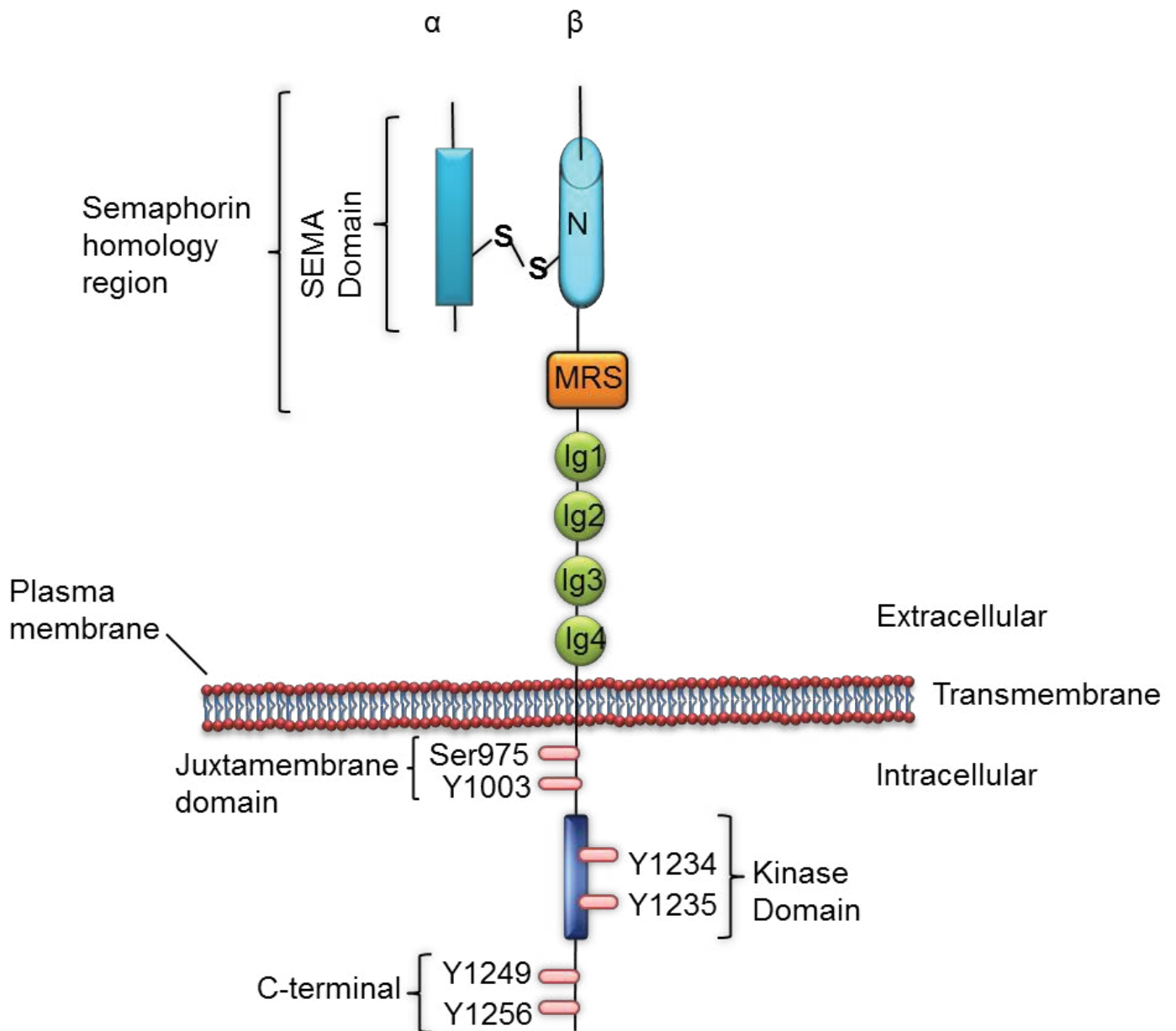
**Figure 2.** Structure of c-Met receptor.

c-Met consists of 50-kDa, totally extracellular α chain and a 140-kDa, transmembran β chain. Extracellular part consists of semaphorin homology region and four Ig repeats. Semaphorin homology region covers SEMA domain and cysteine rich Met related sequence (MRS). SEMA domain contains entire α and N-terminal part of β chains. Intracellular part consists of Juxtamembrane domain with Ser975 and Y1003; Kinase domain with Y1234 and Y1235 and C-terminal tail with Y1249 and Y1256 residues.

c-Met is expressed on various types of cells like epithelial, endothelial, hematopoietic cells, neurons, hepatocytes, melanocytes and cardiomyocytes [82].

## Molecular Mechanisms of HGF/c-Met Signaling Pathway

The action of HGF is initiated upon binding to its receptor c-Met **(Figure 3)**. This results in dimerization of the extracellular domain of the c-Met protein [83, 84, 85]. Subsequently, the intracellular part of c-Met is phosphorylated which leads to the trans-phosphorylation of the catalytic kinase domain and the C-terminal part of c-Met [13, 79, 80]. The phosphorylation leads to activation of diverse intracellular signaling pathways such as MAPKs, PI3K, STAT, NF-κB [1, 13, 14].

The most important of these downstream pathways are the MAPKs. MAPKs can be divided in three subgroups-extracellular signal-regulated kinases (ERKs), p38, and Jun NH2-terminal kinases (JNKs).

ERKs are activated by Ras kinase [86]. Ras is one of the guanosine triphosphate (GTP) binding proteins and activated after trans-phosphorylation of C-terminal part of c-Met in presence of secondary messengers such as Growth Factor Receptor-Bound protein 2 (GRB2). GRB2 can interact directly with c-Met or indirectly via Src-homology-2 domain-containing transforming protein (SHC) [87]. For this transduction c-Met needs intracellular part of CD44v6 via an affiliation with ezrin, radixin, moesin (ERM) proteins and subsequent activation of Raf and MAPK/ERK kinase (MEK)-1,2 kinases [14, 72, 88].
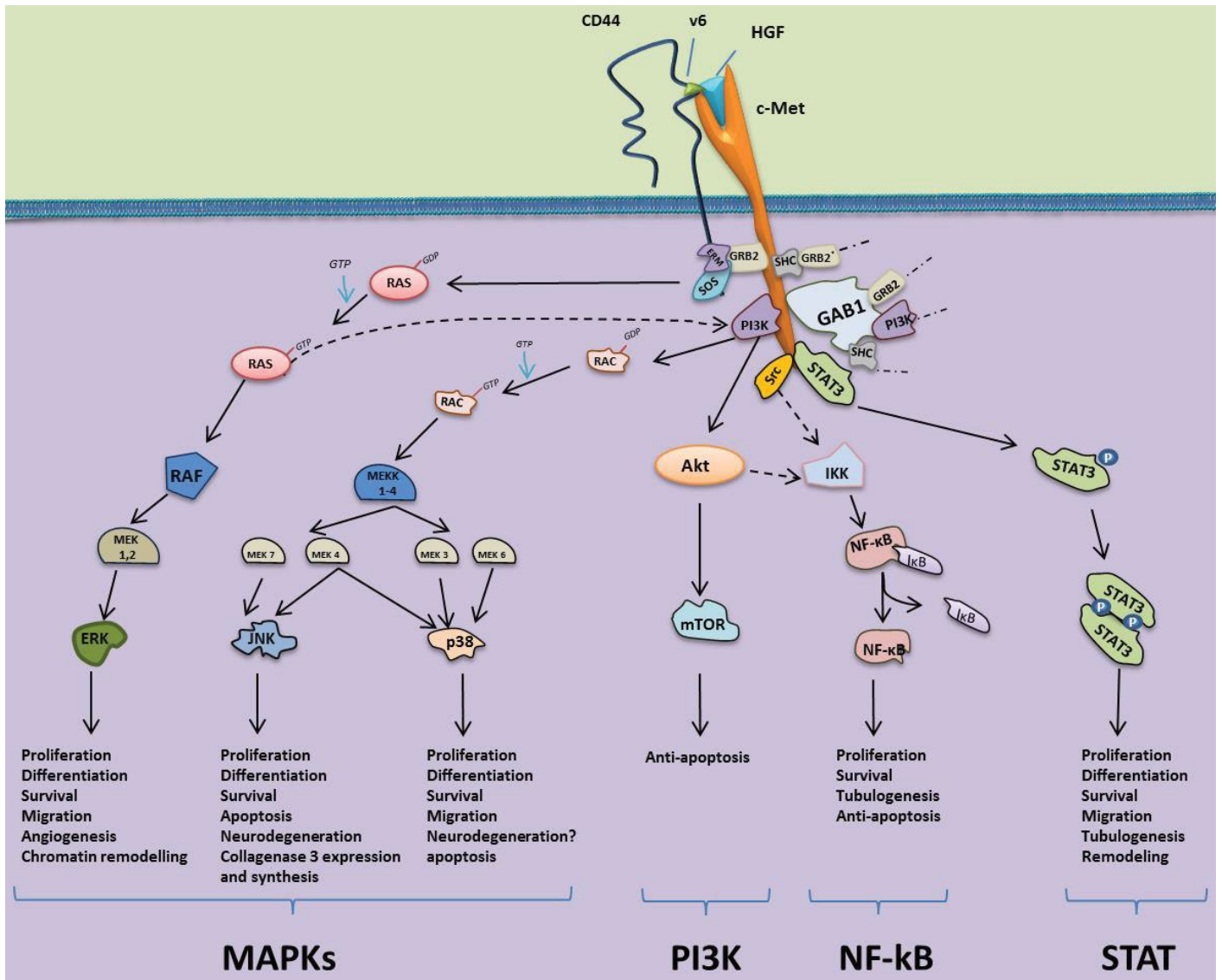
**Figure 3.** Molecular mechanism of HGF signaling pathway.

**MAPKs** subgroups are generally activated by an assistant of adaptors and GTP binding proteins after stimuli. After several trans-phosphorilasation and activation of MAPK cascade, MAPKs subgroups such as ERK, JNK, p38 are able to translocate and activate the substrates such as cytosolic proteins, transcrition factors, etc. As a result, this multiple downstream signal ways activations regulate proliferation, differentiation, survival, migration, angiogenesis, remodeling, apoptosis.

**PI3K** obtains its activation directly upon-binding c-Met terminal tail and/or indirectly by GTP binding protein Ras and controls apoptotic processes.

**STAT** is activated after binding c-Met tail with its SH2 domain and plays important roles in cell proliferation, differentiation, remodeling, migration and c-Met-dependent tubulogenesis.

**NF-kB** is activated through PI3K-Akt way and/or Src pathway and regulates cell proliferation , survival , c-Met-dependent tubulogenesis and anti-apoptosis.

ERKs activate and regulate biological processes such as proliferation, differentiation, survival, migration, angiogenesis, as well as chromatin remodeling in nuclear level [86, 89, 90, 91, 92].

p38s and JNKs are activated by Rac, another GTP binding protein, directly through Phosphatidylinositol-3 kinase (PI3K) or indirectly by the Ras-PI3K mediated way [4, 93, 94, 95, 96]. Both p38s and JNKs Rac initiates MEK-depending stimulation which leads to the phosphorylation of MEK3/MEK6 and MEK4/MEK7 respectively [97]. By this signaling pathway cell differentiation, proliferation migration and apoptosis is regulated [97, 98, 99, 100, 101]. The latter is also responsible for neurodegeneration, as well as collagenase-3 expression and synthesis [91, 93, 95, 97].

PI3K can also activate protein kinase B (Akt) and mechanistic target of rapamycin (mTOR) which regulates anti-apoptotic processes [102, 103].

Transphosphorylation of c-Met also results in activation of STATs. Especially, STAT3 is phosphorylated by binding to the C-terminal end of c-Met via the Src-homology-2 domain (SH2 domain) and subsequently monomer STAT3s dimerizes by recognizing their SH2 domain [15, 104]. Later, homodimer STAT3 is able to translocate to nucleus and regulate cell proliferation, differentiation, remodeling, migration and c-Met-dependent tubulogenesis as well [15, 23, 105, 106, 107].

Additionally, NF-κB is activated after c-Met stimulation as well. This activation can occur through PI3K-Akt signaling pathway and/or Src pathway. NF-κB controls

proliferation, survival, and anti-apoptosis and apoptosis [16, 108, 109].

## Mechanisms of Action in Carcinogenesis

Latest insights suggest that HGF/c-Met signaling plays a key role in carcinogenesis [13, 33, 79, 110, 111, 112]. Its pathophysiological role in tumorigenesis is exerted via activating mutations, amplification, different auto- and paracrine ligand-dependent mechanisms and overexpression of c-Met which can cause ligand-independent spontaneous initiation of the signaling pathway [33, 113]. Interestingly, these findings are more common in adenocarcinomas than sarcomas or other types of cancer [76]. Such pathophysiological findings are detected in different types of cancers, especially in pancreatic cancer [67, 114, 115, 116, 117, 118, 119].

Amplification of c-Met was frequently associated with poor differentiation, poor prognosis and chemo- and radiotherapy resistance [120, 121, 122, 123, 124]. c-Met is rather involved in a late phase of tumor progression as c-Met gene mutations are found in early lesions [125, 126, 127]. Its overexpression associates with cancers with advanced stage, worse prognosis, high metastases, chemo- and radiotherapy resistance [72, 128, 129].

In addition, HGF/c-Met signaling pathway plays a role in tumor angiogenesis [31, 130, 131, 132, 133]. Several experimental and clinical investigations demonstrated that HGF/c-Met stimulates angiogenesis through stimulation of vascular endothelial growth factor (VEGF) signal pathway and its blockade causes downfall in vascularization of tumors. On the other hand, overexpression of VEGF and its receptor had a suppressive effect on HGF/c-Met [22, 134, 135, 136]. Accordingly, inhibition of VEGF activates HGF/c-Met signaling pathway. One explanation might be the anti-vascular effect of the therapy that causes cell hypoxia. Cell hypoxia, however, induces the expression of HGF and c-Met in tumor cells via HIF 1α factor [134, 137, 138, 139]. HGF/c-Met pathway stimulation can results in reduced effect of antiangiogenic therapy. Therefore it was suggested to use combination blocking therapy by using both HGF/c-Met and VEGF inhibitors [130, 140, 141, 142, 143]. In the following we give a more detailed overview on action of HGF/c-Met in pancreatic cancer.

## HGF/c-Met in PDAC

PDAC is an aggressive tumor that is characterized by aggressive infiltration, early metastases, chemoresistance and a distinct desmoplastic reaction and all these characteristics might be mediated by cancer stem cells, which play an important role in pancreatic cancer [37, 72, 144, 145, 146, 147]. Recent evidences suggest that HGF/c-Met signaling pathway has an importance in maintenance of stem cell characteristics and tumorigenic features in PDAC [34, 70, 148]. Overexpression of this stem cell marker has been detected in PDAC CSCs and correlates with poor survival rate and distant metastasis [56, 59, 66, 69, 70, 71, 149]. Furthermore, *in vitro* and *in vivo* investigations

describe that inhibition of this pathway not only declines metastasis, but also local tumor growth [36, 56, 116]. HGF/c-Met signaling is also required for pancreatic CSCs survival, since some *in vivo* studies showed that c-Met inhibition decreased the population of CSCs and decelerated tumor growth [70]. Interestingly, Li *et al.* demonstrated this pathway has a role in the sphere formation which is an evidence of self-renewal ability of CSCs [53, 150]. This *in vitro* experiment showed that c-Met⁺ cells formed spheres, while c-Met⁻ cells did not form spheres [70]. Additionally, the pathway also seems to mediate invasiveness in PDAC [73, 82, 138, 151, 152, 153, 154].

It is known that the desmoplastic reactions of PDAC are responsible for many of the tumors clinical characteristics [155]. Up to 90% of PDAC volume is stromal compartment, which consists of extracellular matrix (ECM), pancreatic stellate cells (PSCs), immune cells, endothelial cells and neurons. [156, 157, 158, 159]. There is increasing interest in the desmoplastic reaction as target for new therapies [155, 160]. Latest reports show that HGF/c-Met signaling pathway is also involved in the interaction between tumor cells and stromal cells and thereby might contribute to the desmoplastic reaction in PDAC [155, 158, 160, 161, 162]. Several studies showed that although PDAC cells do express c-Met, they do not secrete HGF [36, 72]. On the other hand it was demonstrated that cells of the stromal compartment secret HGF and thereby might activate HGF/c-Met signaling in PDAC cells [36, 161]. Interestingly, Niina *et al.* determined *in vivo* HGF expression in PSCs in chronic pancreatitis which is a risk factor for PDAC [163]. Yasui *et al.* described that co-cultivation of fibroblasts and cancer cells could elevate c-Met phosphorylation rate significantly [158]. Interestingly, desmoplastic reactions leads to hypoxia in PDAC environment which also activates HGF/c-Met pathway as already mentioned above [138, 139, 154].

Other studies also support that fibroblasts secrete high amount of HGF in PDAC, subsequently increasing activation of c-Met signaling [164]. This suggests a possible effect of novel cancer therapies that target the cancer environment [155, 160, 161]. Whereas all these data suggest that HGF/c-Met signaling pathway might play an important role in tumor-stromal interaction, the molecular mechanism of this interaction is still unclear and needs further elucidation.

## HGF/c-Met as a Target in PDAC Therapy

Recent investigations demonstrated that inhibition of HGF/c-Met pathway can reduce metastasis in PDAC [36, 56, 116, 165, 166]. Pothula *et al.* showed that HGF inhibition alone had a noteworthy reduction effect on metastases of PDAC [36]. Interestingly, HGF effect on metastasis was not successful when used with gemcitabine. The authors of this study explained this with the stimulating effect of Gemcitabine on cancer cell stemness [36, 48]. Accordingly, it was shown that Gemcitabine treatment increased the number of CSCs in PDAC [48, 167]. Li *et al.* found that treatment with both c-Met inhibitor XL184 and

gemcitabine reduced the cancer growth rate, while groups treated with XL184 or gemcitabine only had the same growth rate as controls [70].

In this regard, it was demonstrated that the inhibition of HGF/c-Met signaling declined the amount of PDAC CSCs and prevented sphere formation [56, 70, 82].

In conclusion, HGF/c-Met signaling might play an important role in different characteristics of PDAC. Accordingly, its inhibition might be an approach in cancer treatment. Different preclinical studies could already give evidence in this regard. Due to the complexity of this pathway, combined therapies seem to have the best effect. As our understanding of its molecular mechanisms is not completely clear, further studies are needed.

## Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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