c-Met: A Promising Therapeutic Target in Bladder Cancer

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Abstract: Mesenchymal-epithelial transition factor (c-Met) belongs to the tyrosine kinase receptor family and is overexpressed in various human cancers. Its ligand is hepatocyte growth factor (HGF), and the HGF/c-Met signaling pathway is involved in a wide range of cellular processes, including cell proliferation, migration, and metastasis. Emerging studies have indicated that c-Met expression is strongly associated with bladder cancer (BCa) development and prognosis. Therefore, c-Met is a potential therapeutic target for BCa treatment. Recently, the aberrant expression of noncoding RNAs was found to play a significant role in tumour progression. There is a close connection between c-Met and noncoding RNA. Herein, we summarized the biological function and prognostic value of c-Met in BCa, as well as its potential role as a drug target. The relation of c-Met and ncRNA was also described in the paper.

Keywords: c-Met, HGF, noncoding RNA, bladder cancer, review

Introduction

Bladder cancer (BCa) is one of the most common malignant carcinomas. According to global cancer statistics, there were 54,939 newly diagnosed cases of BCa in 2018, ranking 12th among all kinds of cancers in both sexes and 6th among those in males.1 BCa is usually classified into two categories: non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC).2 At present, nearly 75% of cases are NMIBC, and 25% are MIBC or metastatic disease.3 The 5-year survival rate for MIBC patients with active treatment is approximately 60%, and the 5-year recurrence rate of NMIBC ranges from 50% to 70%.3 BCa is a complex disease and has been a global burden for a long time. However, current treatments for BCa show limited benefits. Many more studies are required to obtain a more advanced understanding of BCa development and more effective therapeutic strategies. The aberrant activities of mesenchymal-epithelial transition factor (c-Met) have been observed in multiple human malignancies including BCa. In the present study, we reviewed the biological function and prognostic value of c-Met, miRNAs in relation to c-Met, as well as the potential role of c-Met as a drug target in BCa.

The Structure and Biological Function of c-Met

c-Met was first identified in the mid-1980s.4,5 The c-Met-encoding gene is located at chromosome 7q21-31 and is a well-characterized oncogene.6 c-Met, also known as Met, HGFR, AUTS9, RCCP2 and DFN97, belongs to the receptor tyrosine kinase family and is present predominantly in epithelial cells.7 The mature c-Met protein is a disulfide-linked heterodimer composed of a highly glycosylated 45-kDa extracellular α-subunit and a 145-kDa transmembrane β-subunit. The extracellular portions of c-Met consist of three domains, an N-terminal SEMA domain (sematophorin domain), a cysteine-rich portion (plexin sematophorin domain) and four IPT domains (immunoglobulin-like plexin transcription
Hepatocyte growth factor (HGF) is a high-affinity ligand for c-Met and was first discovered in 1984. HGF is the representative of a family of plasminogen-related cytokines named scatter factors and is expressed in cells of mesenchymal origin. The encoding gene of HGF is located at chromosome 7q11.2–21, and the mature form of HGF contains an N-terminal domain, four Kringle domains, and a domain homologous to the chymotrypsin family of serine proteases. Universally, dimerization (the binding of two monomers) is the underlying regulatory mechanism for the activation of tyrosine kinase receptors, and HGF binds to c-Met via this mechanism. HGF contains two receptor-binding sites: a binding site with high affinity for the IPT3 and IPT4 domains of c-Met, and a binding site with low affinity site for the SEMA domain. Upon binding to biologically active HGF, c-Met undergoes dimerization, and Tyr residues Y1234 and Y1235 within the activation loop undergo trans-autophosphorylation. Then, Tyr residues Y1349 and Y1356 within the C-terminal segment undergo autophosphorylation, providing offers binding sites and facilitating the recruitment of downstream signaling effector molecules.

These binding proteins with enzymatic activity include phosphatidylinositol 3-kinase (PI3K), phospholipase C-γ1 (PLC-γ1), the nonreceptor tyrosine kinase Src and signal transducer and activator of transcription 3 (STAT3), as well as adaptor proteins without enzymatic activity, such as growth factor-bound protein 2 (GRB2) and GRB2-associated binding protein 1 (GAB1). These effectors therefore exert effects related to the scattering effect, proliferative action, morphogenetic action and many other biological functions. The downstream signaling pathways include the Ras pathway, PI3K pathway, Wnt/β-catenin signaling pathway and other pathways. Under normal physiological conditions, HGF/c-Met functions in embryogenesis, tissue regeneration, wound healing, and the formation of nerves and muscles, the progression of which is partially mediated by the tumour suppressor p53. In addition, it is well established that c-Met may activate signals in an HGF-independent manner. Accumulating evidence has demonstrated that HGF/c-Met dysregulation and c-Met gene mutations, amplifications and overexpression contribute to a plethora of human diseases, especially cancers, such as lung cancer, liver cancer, and BCa.

### The Role of c-Met in BCa

Early in the 1990s, studies revealed that the HGF/c-Met pathway was involved in BCa development in animal models and in vivo. The expression of HGF/c-Met was increased during the progression of rat bladder carcinogenesis induced with N-butyl-N-(4-hydroxybutyl)-nitrosamine. HGF in rats promoted the proliferation and growth of nontumorigenic cell lines, whereas in tumorigenic cell lines, HGF stimulated cell invasion and migration by either a paracrine or an autocrine mechanism. These results suggested that HGF acted as a mitogen in a nontumorigenic cell line but as an invasion and migration factor in tumorigenic cell lines. Researchers compared the HGF content in urine between patients with BCa and healthy controls and found that HGF was significantly elevated in BCa patients. Therefore, there seems to be a positive association between BCa invasion and HGF content.

c-Met overexpression was observed in 25% (31 of 123) of locally advanced or metastatic bladder urothelial carcinomas, compared with 8.3% (2 of 24) of nonbladder urothelial carcinomas. An analysis of 97 high-grade BCa samples revealed that the frequency of c-Met gene alteration was 2%. Lee et al reviewed several studies and reported genetic aberrations in HGF and c-Met genes at an average combined frequency of 10% in 528 BCa cases. Furthermore, Lee et al measured the cellular c-Met protein content in 12 BCa-derived cell lines, and the values ranged from 12 to 133 ng/mg total protein. The same study demonstrated that autocrine HGF/c-Met signaling was rare in BCa, while paracrine signaling was likely dominant. However, Parr and Jiang revealed a complete HGF autocrine regulatory cycle in BCa cells. Although c-Met and HGF exhibited different expression patterns in different types of BCa cells, these studies revealed enhanced expression of c-Met. c-Met has also been observed to play a facilitating role in BCa cell proliferation, invasion, and migration but an inhibitory role in apoptosis.

Since c-Met and HGF are recognized as characteristic molecules in BCa, more studies have focused on the role of HGF/c-Met in BCa and the underlying mechanisms. The significance of c-Met overexpression was compared with p53 nuclear accumulation (TP53) in primary BCa. The results showed that c-Met expression was strongly correlated with histologic grade, stage classification, tumour size, nodular tumour growth, and disease progression, but not TP53 status.
in BCa. Additionally, c-Met overexpression, but not TP53 status, could indicate a poor long-term survival rate. These findings together demonstrated that c-Met plays a more important role than p53 in bladder carcinogenesis and progression. Antibody arrays were also used to demonstrate that c-Met expression was associated with pathological stage, tumour grade, and the survival rate of BCa patients. Another mechanism was introduced by Sim et al, in which the regulation of the TGFβ signaling pathway plays an essential role in BCa. Specifically, HGF/c-Met activates the phosphorylation of SMURF2 induced by c-SRC, dissociating SMAD7 from SMURF2 and facilitating the interactions between C2 and HECT domains, which silences SMURF2. SMURF2 acts like a switch between MAPK and TGFβ signaling pathways. The inhibition of SMURF2 enhances the membrane TGFβ receptor, and the upregulation of the TGFβ signaling pathway eventually causes EMT and enhances BCa invasiveness.

c-Met belongs to a family of receptor tyrosine kinases (RTKs) that share sequence and structural homology; other family members include RON, AXL and PDGFR. Coexpression of c-Met with RON, AXL or PDGFR is commonly found in urothelial cells. Cheng et al observed that the overexpression of c-Met and RON was positively associated with the histological grade, nonpapillary contour, tumour size and muscle invasion of BCa. The coexpression of c-Met and RON is positively associated with the progression of transitional-cell carcinoma of the bladder and with poor overall survival in patients with superficial BCa. According to reports, the enhanced expression of AXL and PDGFR is correlated with the aggressiveness and prognosis of several tumours. The expression of AXL and PDGFR is greatly altered in BCa and can distinguish between MIBC and NMIBC. Further research showed that expression of c-Met network members (c-Met-AXL-PDGFR) was significantly associated with the disease progression of NMIBC and with the overall survival of MIBC and that c-Met activates AXL and PDGFR-α through a ras- and Src-independent pathway. These findings suggest a new hypothesis that the c-Met-AXL-PDGFR network could be a candidate prognostic marker for predicting BCa development.

Kim et al demonstrated that the downregulation of c-Met could inhibit proliferation and induce cell apoptosis in BCa. Moreover, c-Met silencing suppressed cell motility by downregulating MMP2 and MMP9. Miyata et al found that among different c-Met phosphorylation sites, pY1349 was the only significant factor for high pT stage. Their subsequent studies suggested that two c-Met tyrosine residues, pY1234/pY1235 and pY1349, were related to muscular infiltration and metastasis, while c-Met itself was only significantly associated with muscular infiltration. In contrast, Iyer et al found a nonsignificant association between HGF/c-Met immunoreactivity and tumour stage, grade and overall patient survival. In parallel, Yeh et al found that c-Met expression did not correlate with tumour grade or lymph node involvement. The variability in c-Met expression in BCa could be due to differences in sample size, evaluation methods and tissue sample conditions.

There are various types of BCa, and studies have demonstrated that the HGF/c-Met signaling pathway may be involved in multiple types of BCa. Neuroendocrine BCa is a rare type of BCa. c-Met expression was observed in serum-free cultures, animal models and primary tissue sections; moreover, c-Met inhibitors could greatly decrease tumour growth. HGF could enhance the proliferation, migration, and wound healing of human neurogenic bladder smooth muscle cells and urothelial cells and critically mediate the growth of neuroendocrine BCa spheroids in vitro. Another rare BCa, hepatoid adenocarcinoma of the bladder, also expresses HGF and c-Met. HGF expression was observed in papillary transitional cell carcinoma with notable immunoreactivity but weak immunoreactivity in nodular tumours, while c-Met immunostaining was consistently detected in both papillary and nodular tumours.

In addition to the strong association between cellular c-Met and BCa, urinary soluble c-Met (sMet) and subunits of c-Met might be potential biomarkers for BCa. There is a clear difference in urinary sMet levels between BCa patients and nontumour patients, and urinary sMet levels are able to distinguish MIBC from NMIBC with moderate sensitivity and specificity. Subunits of c-Met are also involved in BCa. P145sMet, the β-subunit of c-Met, in which tyrosine residues 1003, 1234 and 1235 are phosphorylated in the process of the serum-independent growth of human BCa “5637” cell line, is required for “5637” cell survival. This progress is mediated by the transmembrane signaling cascade via EGFR ligand(s). As mentioned above, studies conducted by Miyata et al revealed correlations between c-Met tyrosine residues and BCa progression. Furthermore, they demonstrated possible links between pY1349 c-Met and cancer-related substances such as cyclooxygenase-2 (COX-2), haem oxygenase-1 (HO-1) and programmed death ligand 1 (PD-L1). Intriguingly, the upstream mediator of pY1349 c-Met might be SRY-box 18 (SOX18), which was proven to promote...
carcinogenesis and progression of BCa. In such a study, Huaqi et al observed an augmented level of phosphorylated pY1349 c-Met in SOX18-elevated BCa cells, and after applying cabozantinib, a c-Met suppressor, the migration capability of SOX18-elevated BCa cells was dramatically compromised. 56

Shintani et al took an in-depth look at the relationship between cabozantinib and c-Met in BCa, and their findings suggested that cabozantinib significantly downregulated the expression of matrix metalloproteinase 1 (MMP1), which was induced by HGF/c-Met. 57

The prognostic role of c-Met in BCa has been analysed and confirmed by several studies. Our previous meta-analysis included 8 studies with a total of 1336 cases and demonstrated that c-Met upregulation was associated with shorter overall survival (OS) in BCa patients. Additionally, an immunohistochemical analysis of 26 BCa specimens indicated that the phosphorylation of c-Met mediated by matriptase was strongly correlated with an unfavourable outcome. 58

### Noncoding RNA/c-Met Regulatory Axis in BCa

Dysregulated noncoding RNAs lead to a variety of pathological events and diseases, including BCa. Evidence has shown that miR-409-3p is downregulated in BCa. Enforced expression of miR-409-3p inhibited BCa cell migration and invasion but had no effect on cell proliferation. Mechanistically, miR-409-3p targets the 3’-untranslated region (UTR) of c-Met and reduces the expression of c-Met, which inhibits the downstream proteins MMP2 and MMP9, leading to reduced degradation of the basement membrane and extracellular matrix. Naturally, the overexpression of c-Met could partially reverse miR-409-3p-mediated cancer cell migration and invasion. 59 In addition, the same research group identified that the expression level of miR-101 was negatively correlated with BCa development by targeting c-Met. 60 The migration and invasion of BCa cells are significantly inhibited by decreases in c-Met expression in a miR-101 overexpression-induced manner.

In 2016, Xu et al found that miR-433 was frequently downregulated in BCa tissues. 61 Enhanced expression of miR-433 inhibited cell proliferation, motility and epithelial-mesenchymal transition (EMT). c-Met and CREB1 are direct target genes of miR-433. Silencing c-Met could repress cell motility and EMT by regulating the AKT/GSK-3β/SNAIL signaling pathway, which phenocopied the effect of miR-433 overexpression. Similarly, CREB1 could also exert such a function. CREB1 may regulate c-Met by mediating MITF. Moreover, miR-409-3p was partially involved in the miR-433-induced inhibition of cell migration and invasion. 61 This result implies the possibility of reciprocal regulation among c-Met, miR-433 and miR-409-3p.

There is another c-Met gene network mediated by miRNAs involved in BCa development. Similar to miR-433 and miR-409-3p, miR-323a-3p is downregulated in BCa, and enhanced expression of miR-323a-3p clearly reduced cell motility by regulating EMT progression. 62 Both c-Met and SMAD3 are targeted by miR-323a-3p, which ultimately exerts effects on SNAIL. miR-323a-3p suppression partially rescued the knockdown of c-Met-induced and SMAD3-induced inhibition of EMT progression. Thus, the miR-323a-3p/c-Met/SMAD3/SNAIL circuit is involved in EMT progression in BCa. Moreover, this study revealed the mutual regulation between miR-323a-3p, miR-433, miR-409 and c-Met. 62 In addition, the correlations between miR-323a and c-Met were confirmed by other scientists in different BCa cell lines. 63

The expression of miR-23b and miR-27b was significantly reduced in BCa tissues. 64 Correspondingly, the overexpression of miR-23b and miR-27b exerted inhibitory effects on cell proliferation, migration and invasion. Mechanistically, miR-23b and miR-27b directly repress c-Met and EGFR by binding to the 3’-UTR of the target mRNAs, therefore affecting the downstream signaling pathways.

As mentioned above, miR-433, miR-409-3p and miR-323a-3p all mediate the progression of BCa by targeting c-Met. These miRNAs are all transcribed from the miRNA cluster in the DLK-DIO3-imprinted domain. 65 Therefore, it is reasonable to propose that there are other candidate miRNAs transcribed from the DLK-DIO3-imprinted domain that play important roles in BCa. Li et al demonstrated that miR-381-3p, which is transcribed from the DLK-DIO3-imprinted domain, has great regulatory effects on BCa development. 65 Accordingly, miR-381-3p is downregulated in BCa, while the overexpression of miR-381-3p is able to inhibit BCa cell proliferation and migration. c-Met, together with CDK6 and CCNA2, is directly targeted by miR-381-3p, which explains why miR-381-3p plays an inhibitory role in BCa cell proliferation and migration.
Numerous studies have identified a number of miRNAs involved in BCa progression and metastasis, including miR-34a, miR-206, miR-200, and many others. The target genes of these miRNAs include CDK4 and CDK6. In addition, certain interactions between c-Met and these miRNAs have been identified. c-Met is involved in these miRNA-related circuits and may be a target of these miRNAs. Currently, whether c-Met works in conjunction with miR-34a, miR-206, the miR-200 family, etc. in BCa remains elusive and therefore provides us with a promising research topic. The miRNA/c-Met axis in BCa is shown in Figure 1.

![Figure 1](https://doi.org/10.2147/CMAR.S369175)

**Figure 1** C-Met structure, relevant miRNAs and important signaling pathways involved in HGF/c-Met regulation in BCa. HGF/c-Met-TGFβ signaling: HGF/c-Met activates the phosphorylation of SMURF2 induced by c-SRC, dissociating SMAD7 from SMURF2 and facilitating the interactions between C2 and HECT domains, which in turn puts SMURF2 in a closed inactive status. The silence of SMURF2 stabilizes TβR1 and upregulates the TGFβ signaling pathway and eventually causes EMT.
c-Met and Tumor Microenvironment in BCa

Recent years, numerous studies have demonstrated that tumor microenvironment plays a crucial role in the carcinogenesis and progression in multiple neoplasms including BCa.²⁵ Tao et al discovered an elevated infiltration of CD4+T cells surrounding BCa cells, which promoted the progression of BCa. The underlying mechanisms were revealed that CD4+T cells triggered estrogen receptor beta (ERβ) pathway and ERβ enhanced the expression of c-Met in an IL-1 dependent or independent manner.²⁶ This is the first literature that disclosed the interaction between c-Met and BCa microenvironment, providing us a novel insight into the immunotherapy of BCa.

c-Met Inhibitors in BCa

Generally, c-Met inhibitors could be categorized into three classes: c-Met tyrosine kinase inhibitors (TKIs), HGF antagonists targeting c-Met and HGF-neutralizing antibodies.²⁷ Small molecule TKIs block intracellular signaling pathways in tumor cells, most of which are competitors for ATP binding. Type I inhibitors bind to proteins through a U-shaped structure while type II inhibitors are multi-target agents and function in a more extended spatial conformation. Type III inhibitors are non-ATP competitive agents.²⁸ Table 1 summarized the representative c-Met inhibitors with clinical significance.

Table 1: Representative c-Met Inhibitors with Clinical Significance

| Name            | Type          | Mechanism       | Clinical Trials of c-Met Cancer Types                                                                 | Other Targets            |
|-----------------|---------------|-----------------|--------------------------------------------------------------------------------------------------------|--------------------------|
| Cabozantinib    | Nonselective TKI | ATP competitive | RCC (Phase 2), HCC (Phase 4), Cervical Cancer (Phase 2), CRC (Phase 1), NSCLC (Phase 2), PSCC (Phase 2), Neuroendocrine Tumors (Phase 1), UC (Phase 2), Prostate Cancer (Phase 2), Breast Cancer (Phase 2), Esophageal Cancer (Phase 2), Melanoma (Phase 2), Thyroid Cancer (Phase 3), AML (Phase 1), HNSCC (Phase 2), Pancreatic Cancer (Phase 2), BCa (Phase 2) | VEGFR2, FLT3, KIT, AXL, RET |
| Crizotinib      | Nonselective TKI | ATP competitive | Gastric Cancer (Phase 2), NSCLC (Phase 4), Prostate Cancer (Phase 1), Lymphoma (Phase 2)                 | ALK, ROS1                |
| Foretinib       | Nonselective TKI | ATP competitive | HCC (Phase 1), Breast Cancer (Phase 2), NHSCC (Phase 2), RCC (Phase 2), NSCLC (Phase 1)                 | KDR                      |
| Golvatinib      | Nonselective TKI | ATP competitive | Gastric Cancer (Phase 1), Solid Tumors (Phase 1)                                                       | VEGFR2                   |
| Tivantinib      | Nonselective TKI | Non-ATP competitive | HCC (Phase 3), NSCLC (Phase 2), CRC (Phase 2), Solid Tumors (Phase 1), Pancreatic Neoplasms (Phase 2) | -                        |
| Savolitinib     | Selective TKI  | ATP competitive | NSCLC (Phase 3), Prostate Cancer (Phase 2), Solid Tumors (Phase 1), RCC (Phase 3), CRC (Phase 2), Gastric Adenocarcinoma (Phase 2) | -                        |
| Capmatinib      | Selective TKI  | ATP competitive | HCC (Phase 2), Solid Tumors (Phase 2), Oesophageal Adenocarcinoma (Phase 2), NSCLC (Phase 3),           | -                        |
| Tepotinib       | Selective TKI  | ATP competitive | NSCLC (Phase 2), Solid Tumors (Phase 2), Brain Tumor (Phase 1), HCC (Phase 1)                         | -                        |
| Rilotumumab     | Monoclonal antibody | HGF          | Gastric Cancer (Phase 3), Solid Tumors (Phase 1), NSCLC (Phase 2), Malignant Glioma (Phase 2), Prostate Cancer (Phase 1), RCC (Phase 2) | -                        |
| Ficlatuzumab    | Monoclonal antibody | HGF          | NHSCC (Phase 1), Pancreatic cancer (Phase 1), AML (Phase 1), NSCLC (Phase 2)                           | -                        |
| Onartuzumab     | Monoclonal antibody | c-Met        | Solid Tumors (Phase 3), HCC (Phase 1), Glioblastoma (Phase 2), Solid Tumors (Phase 1), NSCLC (Phase 3), Gastric Cancer (Phase 3), Breast Cancer (Phase 2), CRC (Phase 2) | -                        |

Abbreviations: TKI, tyrosine kinase inhibitor; ATP, adenosine-triphosphate; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; UC, urothelial carcinoma; PSCC, penile squamous cell carcinoma; NSCLC, non-small cell lung cancer; AML, acute myeloid leukemia; HNSCC, Head and neck squamous cell carcinomas; BCa, bladder cancer; HGF, Hepatocyte growth factor; CRC, colorectal cancer; VEGFR2, vascular endothelial growth factor receptor-2; FLT3, FMS-like tyrosine kinase 3; KIT, tyrosine protein kinase kit; AXL, AXL receptor tyrosine kinase; RET, rearranged during transfection; ALK, anaplastic lymphoma kinase; ROS1, proto-oncogene 1, receptor tyrosine kinase; c-Met, mesenchymal-epithelial transition factor.
In BCa, cabozantinib, a nonselective TKI against c-Met and others such as VEGFR2, FLT3, KIT, AXL, and RET is undergoing in-depth clinical research currently. As mentioned above, scientists revealed that cabozantinib could block MMP1 expression mediated by HGF/c-Met. A Phase II clinical trial of cabozantinib and durvalumab combination therapy in patients with metastatic disease after platinum-based chemotherapy initially showed that the combination therapy was safe and achieved an objective response rate of 43.8%. Another TKI with multiple targets including c-Met named crizotinib might be promising in clinical application. A preclinical xenograft study suggested that both crizotinib and cabozantinib significantly suppressed HGF/c-Met induced tumor cell proliferation and invasion in multiple BCa cell lines. Several clinical trials are underway on cabozantinib and crizotinib in BCa treatment, relevant details are listed in Table 2.

### Conclusion

In summary, we evaluated the present knowledge regarding c-Met and its biological and potential therapeutic role in BCa. Currently, c-Met is regarded as a proto-oncogene and facilitates a wide range of biological functions, including cell proliferation, growth, migration, invasion, and angiogenesis, through interaction with its ligand HGF. Enhanced expression of c-Met is positively related to the development of various types of BCa and a poor prognosis. Although there is no final conclusion, it has been observed in many studies that c-Met overexpression is closely related to the histological grade, nonpapillary contour, tumour size and muscle invasion of BCa. Emerging evidence supports that c-Met could be a novel and important biomarker for BCa. As epigenetic regulators, miRNAs perform biological functions by inhibiting gene expression. The aberrant expression of miRNAs has been identified in the development of human diseases, including BCa. Studies have demonstrated that c-Met is the target of various miRNAs. By downregulating the expression of c-Met, aberrantly expressed miRNAs support the survival and metastasis of BCa cells and thus participate in BCa development. Currently, c-Met inhibitors represented by cabozantinib have been widely used in anti-cancer treatment and demonstrates broad prospects for clinical application in BCa.

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### Disclosure

The authors declare that they have no conflicts of interest.

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