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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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REVIEW

Advances in the diagnosis and treatment of MET-variant digestive tract tumors

Chen Zhang, Hu-Ke Dong, Jian-Ming Gao, Qi-Qi Zeng, Jiang-Tao Qiu, Jia-Jia Wang

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Abstract

The receptor tyrosine kinase encoded by the *MET* gene plays an important role in various cellular processes such as growth, survival, migration and angiogenesis, and its abnormal activation is closely related to the occurrence and development of various tumors. This article reviews the recent advances in diagnosis and treatment of MET-variant digestive tract tumors. In terms of diagnosis, the application of next-generation sequencing technology and liquid biopsy technology makes the detection of MET variants more accurate and efficient, providing a reliable basis for individualized treatment. In terms of treatment, MET inhibitors such as crizotinib and cabotinib have shown good efficacy in clinical trials. In addition, the combination of immunotherapy and MET inhibitors also demonstrated potential synergies, further improving the therapeutic effect. However, the complexity and heterogeneity of drug resistance mechanisms are still one of the difficulties in current research. In the future, it is necessary to further deepen the understanding of the mechanism of MET variation and explore

new combination treatment strategies to improve the overall survival rate and quality of life of patients. The diagnosis and treatment of MET-variant digestive tract tumors are moving towards precision and individualization, and have broad application prospects.

Key Words: Digestive tract neoplasms; Interstitial epithelial transfer factor; Targeted therapy; MET variant; Survival prognosis

Core Tip: Our study reviews the progress in the use of MET variation in the diagnosis and treatment of digestive tract tumors and discusses the molecular mechanism of MET variation and its role in the genesis and development of digestive tract tumors. The analysis focused on the potential of MET variants as diagnostic markers and therapeutic targets, covering the latest research results and clinical trial data for MET-based targeted therapies. This paper also summarizes the current challenges and future research directions, aiming to provide new ideas and references for improving the diagnostic accuracy and treatment effectiveness of MET-variant digestive tract tumors.

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INTRODUCTION

Gastrointestinal tumors account for more than 50% of the global incidence and mortality of malignant tumors[1-4]. In addition to conventional surgery, chemotherapy and radiotherapy for the treatment of digestive tract tumors, precise targeted therapy guided by molecular typing has also achieved precise effects in clinical practice[5-8]. In addition to classical RAS, human epidermal growth factor receptor 2 (HER2) and other molecular targets, rare or rare mutation targets such as MET, ROS1, ALK, NTRK and other related drugs have been put on the market one after another and have achieved significant efficacy, becoming one of the current research hotspots in this field[9-12]. This article reviews recent progress in the diagnosis and treatment of MET mutations in patients with digestive tract tumors and explores the application prospects of anti-MET targeted therapy in the field of the digestive tract[13-16].

MET GENE AND ITS EPIDEMIOLOGICAL CHARACTERISTICS

c-MET is a member of the receptor tyrosine kinase family that is expressed mainly in epithelial cells and is structurally divided into an extracellular region, a transmembrane helical domain and an intracellular region, and the extracellular SEMA domain is a key region for ligand binding[17-20]. The hepatocyte growth factor (HGF) synthesized and secreted by mesenchymal cells is the only known ligand of MET[21-24]. HGF and MET receptors bind specifically to the extracellular domain, and the conformation of the MET protein changes to activate the PTK domain of the intracellular tyrosine protein kinase[25-28]. Thus, two phosphorylation sites, Try1234 and Try1235, in the intracellular kinase active region of MET receptors recruit and phosphorylate a variety of effector proteins after phosphorylation[29-32]. Many previous studies have confirmed that the c-MET signaling pathway plays an important role in tumor proliferation, invasion, metastasis, angiogenesis, tumor treatment tolerance, *etc.*, and is abnormally expressed in a variety of digestive tract tumors[33-36] (Figure 1). Therefore, targeted MET therapy may become a new choice for the specific molecular classification of digestive tract tumors[37-40].

The detection rate of *MET* gene variation in patients with solid tumors in China is low, which conforms to the category of rare mutations[41-44]. Large-scale second-generation sequencing (NGS) analysis revealed *MET* gene abnormalities in 10445 cancer patients in China; the incidence of MET amplification was 0.9% (141/10445), and that of exon 14 jump mutations was 0.7%[45-48]. MET amplification is most common in hepatocellular carcinoma (1.7%), gastric cancer (1.3%), and non-small cell lung cancer (NSCLC) (0.7%), whereas MET exon 14 jump mutations are most common in NSCLC (0.5%), hepatocellular carcinoma (0.3%), and colorectal cancer (0.2%)[49-52]. The incidence of MET fusion mutations is even lower[53-56]. A retrospective study in China revealed that the detection rate was only 0.15%, and the heterogeneity of fusion partner genes was very strong[57-60]. National and international guidelines currently identify MET14 exon jump mutations and increased *MET* gene copy number as potential targeted therapeutic molecular features of NSCLC[61-64]. In recent years, major breakthroughs have been made in the precision treatment of digestive tract tumors, including clinical studies on the treatment of rare mutations, including HER2 and MET, which have also achieved satisfactory survival benefits[65-68].

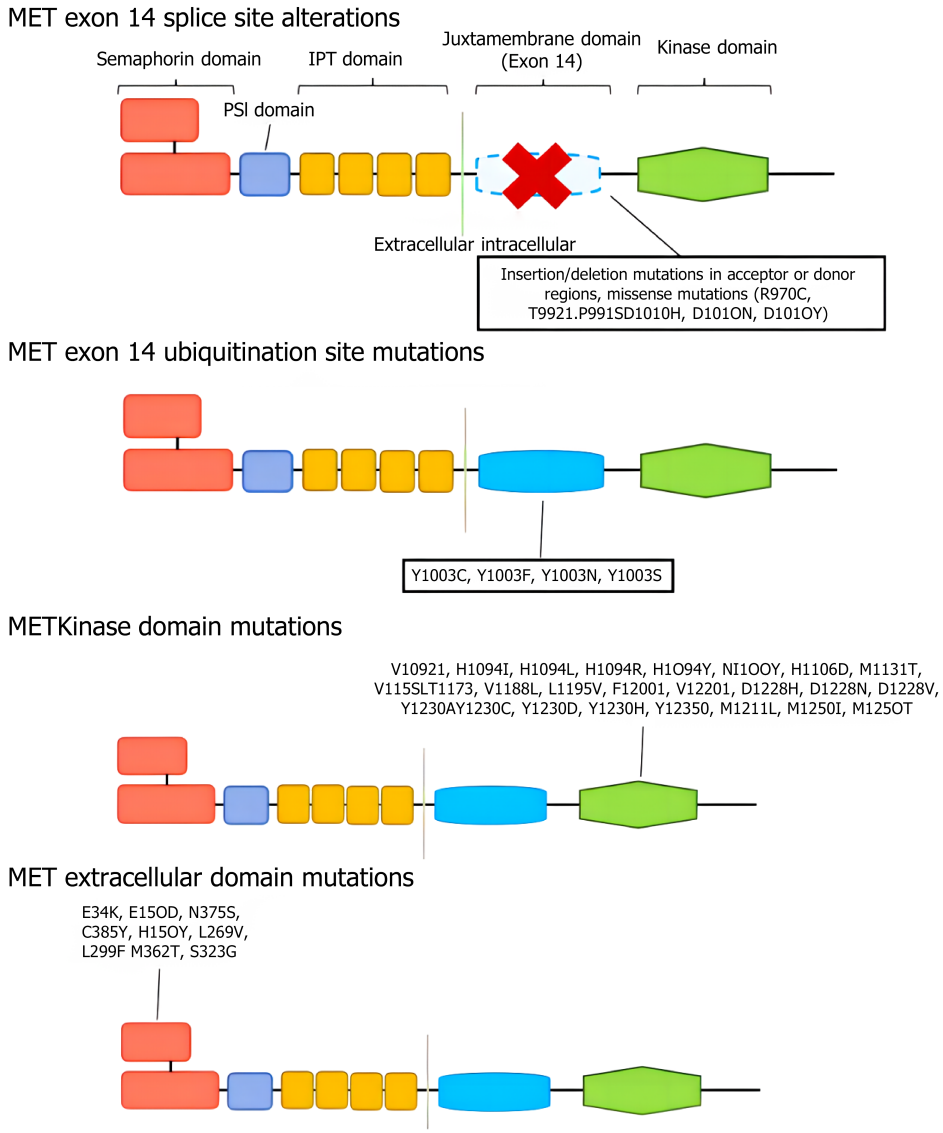

Figure 1 MET mutations. MET mutations include point mutations, insertion mutations, amplification and other types. Common mutation sites are mainly concentrated in tyrosine kinase domains (such as Exon 14 hops) and extracellular domains, which lead to abnormal activation of MET signaling pathway.

Forms of MET variation and its detection

MET variation mainly refers to *MET* gene mutations (mainly MET exon 14 jump mutations), MET gene amplification and MET protein overexpression[69-72]. MET mutations were first identified in patients with hereditary papillary renal cell carcinoma with germline mutations V1092I, H1094R/Y, M1131T, V1188L, V1220I, M1250T, and D1228H/N/V[73-76]. Mutations in the MET kinase domain increase kinase activity, leading to phenotypic transformation or the formation of tumor foci[77-80]. When exon 14 jumps, the Y1003 and c-CblE3 ubiquitin ligase binding sites are missing, resulting in reduced ubiquitination, increased MET stability and continued activation, and the gene eventually becomes a carcinogenic agent[81]. The incidence of MET14 exon spikes in the general population ranges from 0.9% to 4.0%, but the incidence of MET14 exon spikes in lung sarcomatoid carcinoma is greater, ranging from 5% to 32%[82-85]. At present, the detection methods for *MET* gene mutations mainly include NGS and reverse transcription polymerase chain reaction[86-89]. MET amplification is a duplication of a gene or a gene in a region that is not replicated on chromosome 7, resulting in increased MET expression and the activation of downstream signaling pathways independent of ligands. Notably, a gene copy number increase refers to chromosome 7 polysomy and *MET* gene amplification[90-93]. Gene amplification occurs in a variety of tumors, including lung cancer, gastric cancer, bowel cancer, and liver cancer[94-97] (Figure 2). The incidence of primary amplification is approximately 2%-10%, and the prognosis is poor[98-101]. Fluorescence *in situ* hybridization is the current standard method for detecting MET amplification and can detect local amplification and multisoma; real-time fluorescence quantitative polymerase chain reaction and NGS can also be used for detecting MET amplification[102-106]. In different studies, there were differences in the threshold of MET amplification, and MET/CEP7 was reported to have low expression between 1.8 and 2.2, intermediate expression between 2.2 and 5.0, and high expression > 5[107-111]. In general, the greater the degree of MET amplification and the lower the proportion of other driver mutations are, the stronger the driver[112-116]. MET polysoma was defined as MET polysoma when the gene copy number was ≥ 5 but the MET/CEP7 ratio was < 2[117-120]. The increased copy number of the *MET* gene caused by

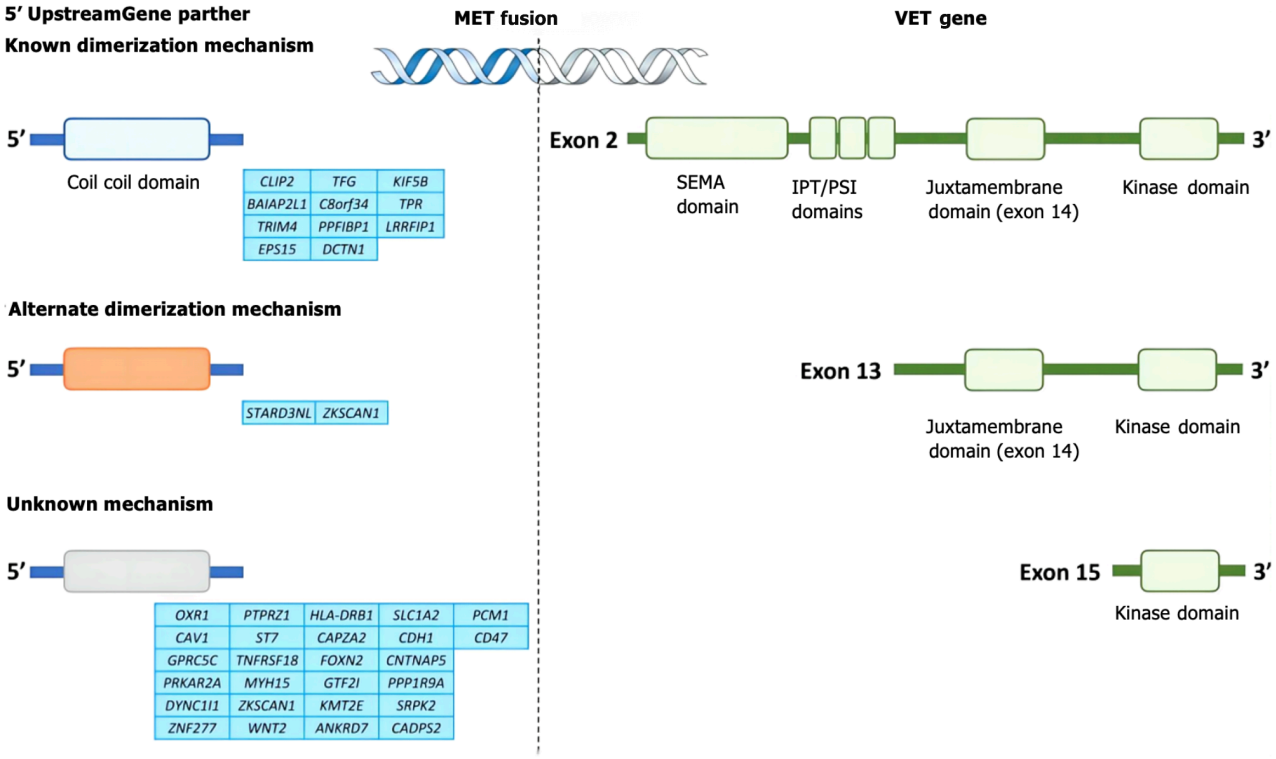

Figure 2 MET fusion. MET fusion refers to the gene fusion between *MET* gene and other genes. Common fusion partner genes include *TPR*, *KIF5B*, *etc*. Fusion mutations usually occur in the tyrosine kinase domain of MET, resulting in its continuous activation.

polysomy cannot be identified as a driver of gene variation[121-124] (Figure 3). MET protein overexpression may be present regardless of whether the *MET* gene is abnormal. MET can induce cancer cell proliferation, reduce apoptosis and promote metastasis under hypoxia and/or inflammation[125-128]. Thus, tumors may rely on MET signaling even in the absence of genomic drivers such as MET amplification, mutation, or fusion[129-131]. The incidence of MET protein overexpression is greater than those of MET exon 14 jump mutation and *MET* gene amplification, which are associated with poor patient prognosis. MET protein expression can be evaluated *via* immunohistochemistry[132]. We believe that the definition and criteria for MET variation in gastrointestinal tumors can be compared with those for NSCLC, and routine screening for rare mutations, including MET, should be conducted[133-137].

EFFECT OF MET VARIATION ON THE PROGNOSIS AND TREATMENT OF DIGESTIVE TRACT TUMORS

The incidence of MET amplification is approximately 5% to 8% in gastric cancer patients and approximately 15% in diffuse gastric cancer patients[138-140]. MET protein overexpression is highly common in enteric gastric cancer (63% overexpression rate; previous reports vary and may be related to different detection methods). Met-amplified gastric cancer is characterized by low differentiation of tumor cells, easy peritoneal metastasis and malignant lymphangitis[141]. Moreover, a previous study revealed that the MET status of approximately 35% of gastric cancer patients changes with the course of treatment, requiring dynamic detection[142-145]. MET amplification is often accompanied by HER2 overexpression in gastric cancer, and co-expression of MET and HER2 can synergistically enhance tumor invasion, invasion and metastasis, which is an important factor for poor prognosis (Figure 4). According to a retrospective analysis of 233 patients, survival was 24.6 months in the non-MET-amplified group and 9.3 months in the MET-amplified group [hazard ratio (HR) = 1.6, 95% confidence interval (CI): 1.0-2.5, P = 0.049], suggesting shorter survival and a worse prognosis in patients with MET-amplified gastric cancer[146-149]. Abnormal activation of the MET signaling pathway in liver cancer is due mainly to ligand binding, which leads to its overexpression, but its high expression rate is due to differences in detection methods (the subjective influence of immunohistochemistry is relatively large), resulting in a large variation in its incidence rate (25.4%-61.2%)[150]. A meta-analysis evaluating the prognostic value of MET overexpression in 1408 patients who underwent liver resection revealed that progression-free survival (PFS) and overall survival (OS) were significantly worse in patients with high MET expression than in those with low MET expression (HR = 1.26, P = 0.03; HR = 1.16, P = 0.01), suggesting that MET overexpression may be a poor prognostic indicator of liver cancer[151-154]. There are also clinical data showing that patients with high MET expression in liver cancer are more likely to develop intrahepatic metastasis[155-158]. The high expression of MET in patients with early colorectal cancer is related to the depth of intestinal wall lymph node invasion and regional lymph node metastasis, and some studies have shown that the high expression of MET is related to clinical characteristics such as tumor invasion and liver metastasis. Some scholars have analyzed the changes in gene expression in the ctDNA of advanced colorectal cancer patients who previously

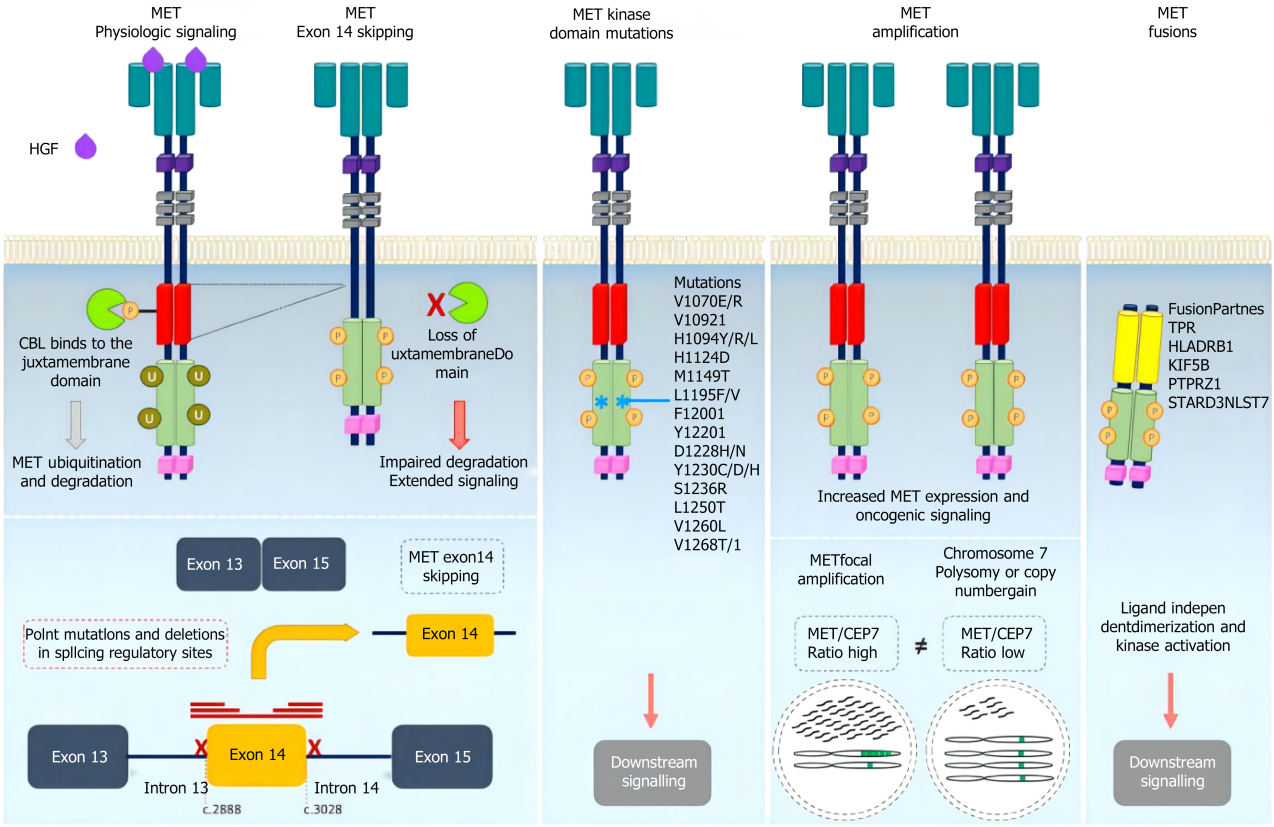

Figure 3 Mechanisms of MET oncogenic activation. The mechanism of MET carcinogenic activation mainly includes gene mutation, gene amplification and fusion, *etc*. Through abnormal activation of MET receptor tyrosine kinase, downstream signaling pathways such as RAS/mitogen-activated protein kinase, phosphoinositide 3-kinase/protein kinase B and Janus kinase/signal transducer and activator of transcription are triggered to promote cell proliferation, migration and anti-apoptosis. HGF: Hepatocyte growth factor.

received anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapy and reported that, after treatment with anti-EGFR monoantibodies, especially in resistant patients, the number of copies of the *MET* gene significantly increased compared with that in patients who were not exposed to EGFR monoantibodies[159-162]. MET amplification is considered to be one of the main mechanisms of retroline resistance to EGFR monoantibodies in metastatic colorectal cancer[163-166] (Figure 5).

Research progress on MET variation in digestive tract tumors

MET inhibitors include highly selective tyrosine kinase inhibitors (TKIs) (sevotinib, tepotinib, camatinib, *etc*.), pantargeted TKIs (crizotinib), and monoclonal antibodies (TKIs, *etc*.)[163]. Preclinical studies suggest that the MET inhibitor sevotinib has a dose-dependent killing effect on MET-amplified gastric cancer, and this inhibition is more significant when it is combined with chemotherapy[164-167]. The antitumor efficacy of sevoflurane has been preliminarily demonstrated in a human tumor xenotransplantation (PDX) model of gastric cancer with MET overexpression [168-170]. The VIKTORY clinical trial explored the efficacy of single-agent sevotinib in patients with MET-amplified gastric cancer, and the results revealed that the objective response rate of single-agent sevotinib reached 50%; 10 patients achieved a partial response, and 1 patient achieved a complete response, among which the second-line PFS duration was 4-6 months, and the efficacy was obvious[171-174]. Subgroup analysis revealed that patients with a MET copy number > 10 had a better response rate to sevoflurane, and the MET copy number was strongly associated with PFS duration[175-178]. Crizotinib has also been used to treat advanced gastric cancer patients with MET amplification and liver metastasis who achieved complete remission of liver lesions after 2 months of treatment and a PFS duration of up to 20 months[179, 180]. In addition to the effects of sevotinib, the effects of other MET inhibitors, including monoclonal antibodies, have also been explored in patients with MET-variant gastric cancer[148-151] (Figure 6). In general, the efficacy of specific TKIs is greater than that of monoclonal antibodies. However, at present, these are small sample size studies, and more high-level clinical studies are needed to demonstrate its efficacy and safety[181-184].

DISCUSSION

MET is a therapeutic target for liver cancer, but few monoclonal antibodies and HGF inhibitors have been developed, and related clinical studies have focused on MET TKIs[185-188]. As a highly selective MET TKI, tivantinib significantly improved PFS and OS (2.7 months *vs* 1.4 months and 7.2 months *vs* 3.8 months, respectively) compared with placebo in a

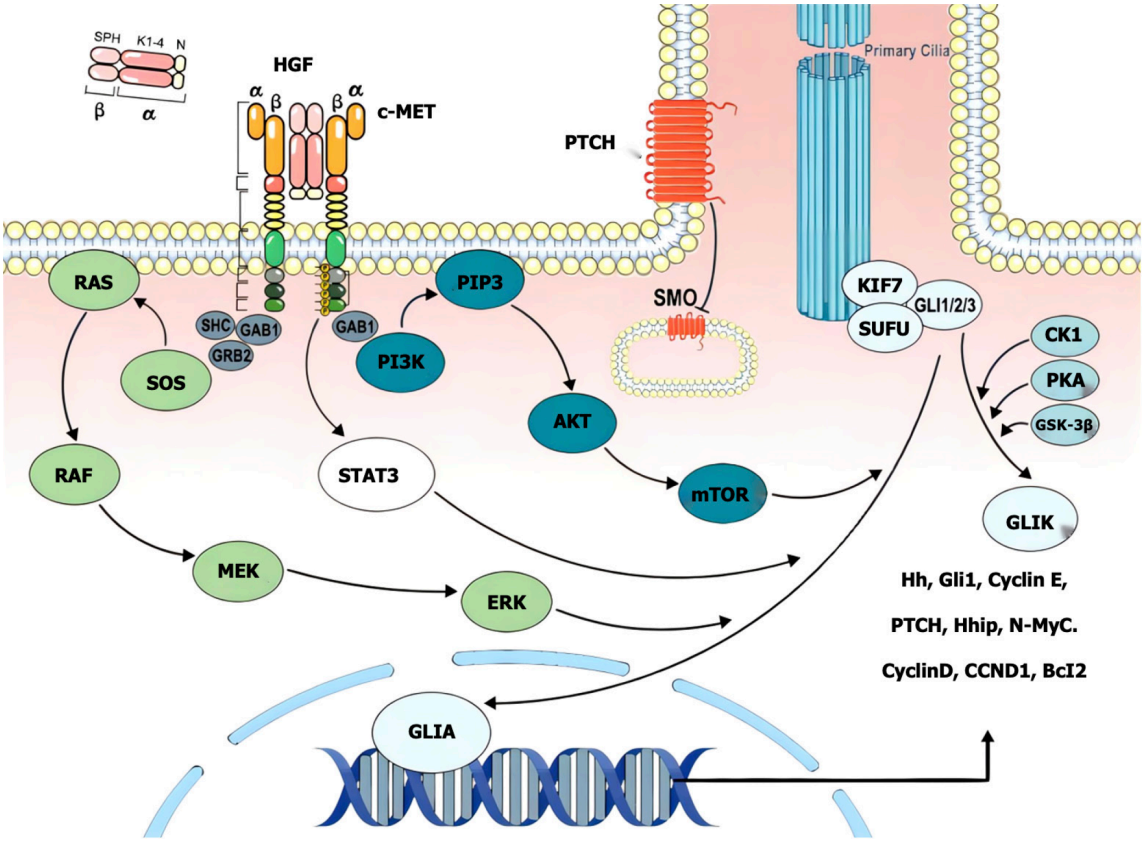

Figure 4 The hepatocyte growth factor/c-Met axis activates the Hedgehog pathway through downstream signaling. The hepatocyte growth factor (HGF)/c-Met axis activates the Hedgehog pathway through its downstream signaling pathway. After binding to the c-Met receptor, hepatocyte growth factor activates the extracellular signal-regulated kinase 1/2 and protein kinase B signaling pathways, further promoting the activation of GLI transcription factors, and thereby initiating the transcription activity of the Hedgehog pathway. HGF: Hepatocyte growth factor; Hh: Hedgehog; SPH: Secreted protein, acidic and rich in cysteine; MEK: Mitogen-activated protein/extracellular signal-regulated kinase; ERK: Extracellular signal-regulated kinase; STAT3: Signal transducer and activator of transcription 3; SHC: Src homology 2 domain containing; GAB: Grb2-associated binder; PI3K: Phosphoinositide 3-kinase; KIF7: Kinesin family member 7; GLI: GLI family zinc finger transcription factor; PKA: Protein kinase A; GSK-3β: Glycogen synthase kinase 3 β; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; GLIA: Glioma-associated oncogene homolog; Bcl: B-cell lymphoma; CCND: Cyclin D.

phase II clinical study of second-line MET TKIs for highly expressed MET liver cancer[189-191]. Therefore, screening the right people or finding new combinations may be effective[192,193]. Therefore, screening the right people or finding new combinations might be useful. Preclinical studies have shown that hypoxia induced by inhibition of the vascular endothelial growth factor signaling pathway induces hypoxia-inducible factor-1 nuclear aggregation, leading to increased MET expression[194]. CELESTIAL clinical studies have shown that cabotinib is a nonselective multitarget inhibitor with anti-MET and angiogenic effects and is effective in patients with liver cancer who have failed sorafenib treatment and received more than 2 systems, with initial results indicating improved OS in patients[195-198]. Although there are no large-scale clinical studies demonstrating the efficacy and safety of MET inhibitors in the field of liver cancer, MET inhibitors may be a promising choice for liver cancer patients with specific molecular types, such as those with high MET expression[199-202].

Crizotinib, camatinib, and tevantinib have been used as selective MET inhibitors in preclinical and in-clinical trials for the treatment of MET-variant colorectal cancer[203-205]. Scholars have reported that crizotinib can effectively improve the sensitivity of cetuximab-resistant cell lines to radiotherapy both *in vivo* and *in vitro*[206]. A clinical study of MET-positive metastatic colorectal cancer (NCT02205398) revealed that the combination of carmatinib and cetuximab in four patients with EGFR-resistant MET-positive colorectal cancer achieved a partial response and was well tolerated. However, tivantinib in combination with cetuximab failed to significantly improve PFS in patients with colorectal cancer, and adverse effects persisted. The antitumor activities of SU11274, PHA665752, nororitin and other MET inhibitors have been confirmed in preclinical studies of colorectal cancer, but relevant clinical studies are lacking. The effectiveness of MET inhibitors in colon cancer patients with MET variants still needs to be further explored.

CONCLUSION

Through a systematic review of the progress in the diagnosis and treatment of MET-variant digestive tract tumors, we found that the molecular mechanisms of MET-variant digestive tract tumors are complex and diverse and show specificity for different tumor types. Therapeutic strategies targeting MET, including small molecule inhibitors and

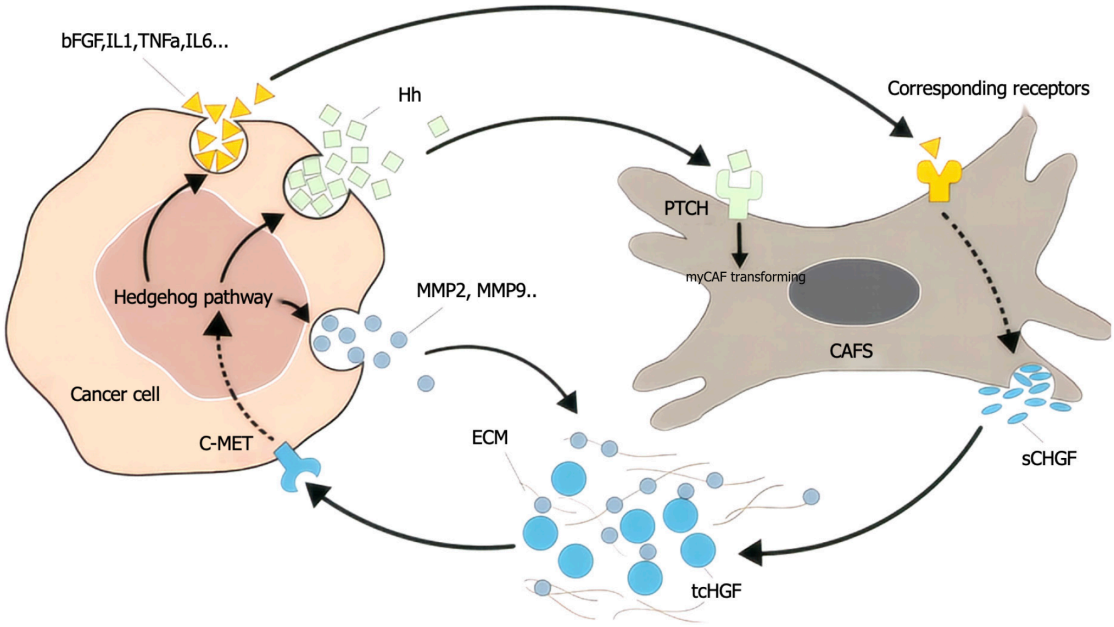

Figure 5 Hepatocyte growth factor and Hedgehog loops between cancer cells and cancer-associated fibroblasts. Hepatocyte growth factor (HGF) and Hedgehog (Hh) pathways form a feedback loop between cancer cells and cancer-associated fibroblasts. Cancer-associated fibroblasts secrete hepatocyte growth factor, activate c-Met receptors in cancer cells, trigger downstream signaling pathways, and thus enhance the proliferation, migration, and invasion of cancer cells. bFGF: Basic fibroblast growth factor; IL: Interleukin; TNF: Tumor necrosis factor; Hh: Hedgehog; MMP: Matrix metalloproteinase; ECM: Extracellular matrix; tcHGF: Truncated hepatocyte growth factor; CAFS: Cancer-associated fibroblasts; sCHGF: Soluble hepatocyte growth factor.

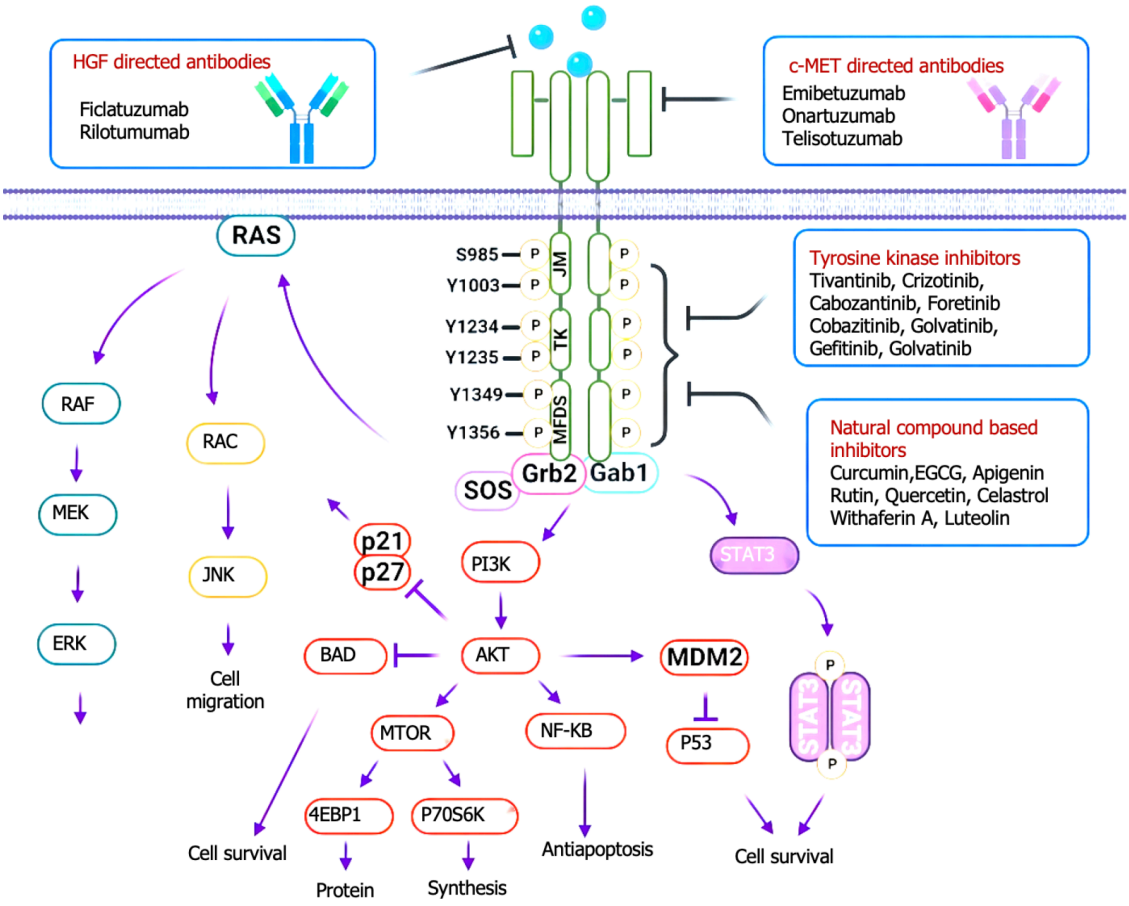

Figure 6 The c-MET pathway relays downstream signals to activate multiple oncogenic events to promote cell proliferation, migration, protein synthesis, and antiapoptosis. The c-MET pathway transmits downstream signals by activating its receptor tyrosine kinase, triggering multiple carcinogenic events. This pathway activates signaling pathways such as RAS/mitogen-activated protein kinase, phosphoinositide 3-kinase/protein kinase B, and

promotes cell proliferation, migration, protein synthesis, and anti-apoptosis. HGF: Hepatocyte growth factor; MEK: Mitogen-activated protein/extracellular signal-regulated kinase; ERK: Extracellular signal-regulated kinase; RAC: Ras-related C3 botulinum toxin substrate; JNK: Jun N-terminal kinase; BAD: Bcl-2-associated death promoter; mTOR: Mechanistic target of rapamycin; Grb2: Growth factor receptor-bound protein 2; Gab1: Grb2-associated binder 1; STAT3: Signal transducer and activator of transcription 3; MDM2: Mouse double minute 2; PI3K: Phosphoinositide 3-kinase; AKT: Protein kinase B; NF-κB: Nuclear factor kappa B; EGCG: Epigallocatechin gallate.

immunotherapy, have shown significant clinical efficacy. However, drug resistance and individual variability remain major challenges. Future research should focus on precision medicine and optimize individualized treatment plans by integrating multilevel data such as genomic and transcriptomic data, thereby improving patient survival and quality of life.

FOOTNOTES

Author contributions: Zhang C and Dong HK wrote the manuscript, they contributed equally to this study, and they are the co-first authors of this manuscript; Gao JM, Zeng QQ, and Qiu JT collected the data; Wang JJ guided the study. All authors reviewed, edited, and approved the final manuscript and revised it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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