**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 62149

**Manuscript Type:** MINIREVIEWS

**RON in hepatobiliary and pancreatic cancers: Pathogenesis and potential therapeutic targets**

Chen SL *et al*. RON in hepatobiliary and pancreatic cancers

Shao-Long Chen, Guo-Ping Wang, Dan-Rong Shi, Shu-Hao Yao, Ke-Da Chen, Hang-Ping Yao

**Shao-Long Chen, Ke-Da Chen,** Shulan International Medical College, Zhejiang Shuren University, Hangzhou 310000, Zhejiang Province, China

**Guo-Ping Wang,** Department of Surgical Oncology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310000, Zhejiang Province, China

**Dan-Rong Shi, Hang-Ping Yao,** State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310000, Zhejiang Province, China

**Shu-Hao Yao,** Department of Stomatology, Wenzhou Medical University Renji College, Wenzhou 325035, Zhejiang Province, China

**Author contributions:** Chen SL, Wang GP, Shi DR, Yao SH, Chen KD, and Yao HP discussed the necessity of writing this manuscript; Chen SL and Yao HP wrote the original draft; Chen SL, Wang GP, Shi DR, Yao SH, Chen KD, and Yao HP reviewed the draft with detailed comments; Chen SL and Yao HP made revisions to the manuscript; all authors read and approved the final manuscript for submission.

**Supported by** National Natural Sciences Foundation of China, No. 81872883; and Zhejiang Major Medical Health & Sciences Technology Foundation Projects, No. WKJ-ZJ-13.

**Corresponding author: Hang-Ping Yao, PhD, Professor,** State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, No. 79 Qingchun Road, Shangcheng District, Hangzhou 310000, Zhejiang Province, China. yaohangping@zju.edu.cn

**Received:** December 31, 2020

**Revised:** March 4, 2021

**Accepted:** April 9, 2021

**Published online:** May 28, 2021

**Abstract**

The receptor protein tyrosine kinase RON belongs to the c-MET proto-oncogene family. Research has shown that RON has a role in cancer pathogenesis, which places RON on the frontline of the development of novel cancer therapeutic strategies. Hepatobiliary and pancreatic (HBP) cancers have a poor prognosis, being reported as having higher rates of cancer-related death. Therefore, to combat these malignant diseases, the mechanism underlying the aberrant expression and signaling of RON in HBP cancer pathogenesis, and the development of RON as a drug target for therapeutic intervention should be investigated. Abnormal RON expression and signaling have been identified in HBP cancers, and also act as tumorigenic determinants for HBP cancer malignant behaviors. In addition, RON is emerging as an important mediator of the clinical prognosis of HBP cancers. Thus, not only is RON significant in HBP cancers, but also RON‑targeted therapeutics could be developed to treat these cancers, for example, therapeutic monoclonal antibodies and small-molecule inhibitors. Among them, antibody-drug conjugates have become increasingly popular in current research and their potential as novel anti-cancer biotherapeutics will be determined in future clinical trials.

**Key Words:** RON; Signal transduction; Hepatobiliary; Pancreatic neoplasms; Molecular targeted therapy

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Chen SL, Wang GP, Shi DR, Yao SH, Chen KD, Yao HP. RON in hepatobiliary and pancreatic cancers: Pathogenesis and potential therapeutic targets. *World J Gastroenterol* 2021; 27(20): 2507-2520

**URL:** https://www.wjgnet.com/1007-9327/full/v27/i20/2507.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v27.i20.2507

**Core Tip:** The role of RON in cancer pathogenesis has received increasing research attention. Hepatobiliary and pancreatic (HBP) cancers have a poor prognosis, being reported as having higher rates of cancer-related death because of their high rates of recurrence, metastasis, and invasiveness, and their lack of sensitivity to chemotherapy. In this review, we discuss how RON functions in HBP cancer pathogenesis, as well as its potential role as a therapeutic target in HBP cancers.

**INTRODUCTION**

RON receptor tyrosine kinase (RTK; also known as MST1R) was first identified in 1993 in a cDNA library from human epithelial cells[1]. RON belongs to the family of c-MET proto-oncogenes[2]. This RTK family only has two members, RON and Met, which share only 34% overall homology; however, the tyrosine kinase region of the receptors is quite similar at 80% homology[3]. In 1994, a mouse cDNA was cloned that encoded a homolog of RON, which was termed stem cell-derived tyrosine kinase receptor[4]. *RON* is located at human chromosome 3p21 and this gene shows high conservation in different species, including xenopus, zebrafish, chicken, cats, human, and mouse[4-11]. The RON receptor is initially synthesized as a biologically inactive single-chain precursor (pro-RON), then cleaved into a 145 kDa β-chain and a 35 kDa extracellular alpha chain, which are linked by a disulfide bond, forming the mature receptor. In 1994, the physiological ligand of RON was identified as macrophage-stimulating protein (MSP) [also called hepatocyte growth factor (HGF)-like protein], establishing the MSP-RON signaling system[12-15]. MSP is a member of the plasminogen-related kringle protein family[16,17]. The human *MSP* gene is also located at chromosome 3p21 and is evolutionarily conserved in different species, similar to RON. The main source of MSP is hepatocytes and MSP circulates in the blood as pro-MSP, which is a biologically inactive single-chain precursor. After subsequent proteolytic conversion, the active mature MSP consists of the disulfide-linked alpha subunit and β-chain. The RON receptor high affinity binding site is in the β-chain and RON activity is regulated by the alpha chain[18]. The binding of MSP to RON induces RON dimerization, which activates multiple downstream signaling pathways, leading to RON-mediated cell growth, survival, and invasiveness[19,20].

In the last two decades, increased research has focused on the tumorigenic and therapeutic roles of RON signaling. Although there have been few studies concerning pathology-related changes in MSP expression, numerous studies regarding aberrant RON activation in various types of tumors have been published, including RON protein overexpression[21-28], oncogenic variant generation[29-39], and persistent activation of downstream signaling pathways[21-39]. In addition, tumorigenic progression and malignancy are associated with functional crosstalk between signaling proteins and RON. In clinical application, increased RON expression can be used for prognostic evaluation of patient survival and disease progression. Hepatobiliary and pancreatic (HBP) cancers have a poor outcome, with high rates of cancer-related death because of their high incidences of recurrence, metastasis, and invasiveness, and their lack of sensitivity to chemotherapy[40]. Complete surgical resection remains the most effective treatment for HBP cancers[40]. Among these cancers, the 5-year survival rate of liver cancer is approximately 30%, whereas in biliary tract cancer and pancreatic cancer, it is less than 30% and less than 10%, respectively[41]. The high death rate of pancreatic cancer is caused by the lack of early diagnosis and effective treatment. In pancreatic cancer, most cases are diagnosed when the disease is already at an advanced stage, and only 20% or less of patients present with potentially curable localized tumors amenable to surgical extirpation[42]. Thus, the identification of a novel potential therapeutic strategy is urgently required. Growing evidence suggests a close relationship between HBP cancers and RON dysregulation[24,43,44]. Thus, the present review primarily focuses on the role of RON in the pathogenesis of cancer, especially HBP cancers. Moreover, we summarize the latest progress in the development of strategies targeting RON as potential HBP cancer therapy.

**ROLES OF RON AND c-MET IN CARCINOGENESIS**

RON and c-MET, both of which are members of the semaphorin family of transmembrane receptor tyrosine kinases, share similar structural and biochemical properties[45]. The proteins exist as heterodimers comprising extracellular and transmembrane chains that are linked by disulfide bonds. The RON and c-MET extracellular sequences possess very similar functional domains, including SEMA, which regulates phosphorylation, receptor dimerization, and ligand binding. RON and c-MET are activated by their respective ligands: MSP for RON and HGF for c-MET. c-MET and HGF are expressed in a variety of cell and tissue types. Contrastingly, RON is restricted tightly to epithelial origin cells, whereas liver cells are the major source of its ligand, MSP[46]. Independent or ligand-dependent activation of RON and c-MET induces matrix invasion, cell migration, and cell proliferation, all of which are crucial for embryogenesis, wound healing, and tumorigenesis.

Increasing evidence has identified the role of RON and c-Met in the pathogenesis of cancer[47]. For example, c-MET and RON overexpression was observed in a variety of primary and metastatic tumors, leading to the activation of aberrant downstream signaling, which contributes to cancer development and progression. Moreover, clinical studies have validated that increased expression of RON and c-MET is a prognostic factor to predict the survival rate and disease progression in certain patients with cancer[48,49]. Moreover, activation of RON and c-MET promotes a cancer cell malignant phenotype. Increased RON and c-MET expression drives tumor cells to undergo epithelial to mesenchymal transition (EMT), which is characterized by epithelial feature loss and the gain of mesenchymal characteristics[12,50]. Increased c-MET and RON expression also contributes to acquired chemoresistance[51]. Given the above role of the increased expression of c-MET and RON in cancer pathogenesis, targeting RON and c-MET represents a promising cancer therapy strategy.

**RON ACTIVATION AND SIGNALING PATHWAY MECHANISMS**

Epithelial cells in the skin, adrenal gland, bone, brain, kidney, gut, lung, and liver express low levels of RON[12]. The action of RON plays a key role in the motility of epithelial cells, enhancement of adhesion, sperm motility in the epididymis, and embryonic development, as well as the regulation of inflammatory responses[52]. Under physiological conditions, the main cause of RON activation is stimulation of its ligand, MSP[12]. Moreover, three other biochemical events activate RON in tumors: RON overexpression, generation of oncogenic RON variants, and RON transactivation (Figure 1). The RON receptor consists of three essential regions: The extracellular domain that recognizes its ligand, the transmembrane domain that anchors the receptor to the membrane, and the intracellular domain that exerts the kinase activity (Figure 1)[53]. The first step for the activation of RON is dimerization at the cell surface, which is caused by the binding of MSP to the extracellular domain containing the specific ligand-binding site, likely resulting in a conformational change in the RON receptor. This activation leads to autophosphorylation at two tyrosine residues (Tyr1238 and Tyr1239) located in the A-loop (Phe1227-Pro1250) of the kinase domain. Phosphorylation of these regulatory residues leads to tyrosine kinase function activation, inducing further phosphorylation of residues Tyr1353 and Tyr1360 located in the C-terminal docking site. This then recruits the cytoplasmic molecules growth factor receptor-bound protein 2 (GRB2) and Son of Sevenless. In addition, the ubiquitin ligase, casitas B-lineage lymphoma (CBL), binds to the docking site to act as a negative modulator.

The interaction of RON with adaptor proteins, such as β-arrestin-1 and GRB2, represents the first step in the bridging of downstream signaling cascades and RON activation. *Via* its C-terminal docking site, RON interacts with a variety of cytoplasmic effector molecules, such as phospholipase C gamma, phosphatidylinositol-4,5-Bisphosphate 3-kinase (PI-3 kinase), Src (SRC proto-oncogene, non-receptor tyrosine kinase), tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein (14-3-3), CBL protooncogene (c-Cbl), heat shock protein family A (Hsp70) member 8 (HSC70), integrin-β4, plectin, and protein phosphatase 1. The classical PI-3 kinase- protein kinase B (PI-3K-AKT) and RAS-mitogen-activated protein kinase (RAS-MAPK) pathways are triggered by the interaction of RON’s docking site with downstream signaling proteins. PI-3K-AKT and RAS-MAPK pathways mediate many biological activities, including increased proliferation and survival, EMT, motile-invasive activity, and chemoresistance. The signaling pathways of RON also play a part in regulating tumorigenic activity. Among them, PI-3K-AKT and RAS-MAPK pathway coordinated activation plays a crucial role in EMT *via* increased cellular motility[15,22,54,55]. Studies using the MDCK cell model showed that EMT mediated by RON is associated with decreased E-Cadherin expression and unregulated vimentin expression, under mediation by RAS-MAPK signaling[56,57]. The major protein that links EMT to RON signaling is ribosomal protein S6 kinase-2, which is an intermediate in the MAPK pathway. RON-mediated PI-3K-AKT signaling is also involved in invasive growth, including increased epithelial cell matrix invasion, migration, and adhesion *in vitro* and distant metastasis and tumor cell invasion *in vivo*[54,55].

**ABERRANT RON SIGNALING AND EXPRESSION IN CANCER PATHOGENESIS**

In general, normal epithelial cells, including those from the colon, lung, and breast, express low levels of RON; however, cells of a mesenchymal origin do not express RON[12,58]. RON activation in tumors is frequently the result of receptor overexpression, in contrast to classical MSP binding. Dysregulated RON activation and expression were detected in many types of cancers and have prognostic significance for patient survival. Results from the majority of published studies show that RON expression dysregulation is characterized mainly by elevated expression of wild-type RON and the production of active isoforms, ultimately leading to persistent activation of downstream signaling cascades[12]. There have been reports of *RON* amplification and point mutation; however, this kind of genetic alteration is observed rarely[26]. The relationships between cancer pathogenesis and dysregulated RON signaling and expression were proven *via* functional studies using immunohistochemical (IHC) staining of tumor specimens and cancer cell lines. The first report of wild-type RON overexpression in cancerous tissue was in primary breast cancer samples. Thereafter, IHC staining has further detected wild-type RON in thyroid, bladder, adrenal gland, head and neck, uterus, skin, lung, kidney, pancreatic, colorectal, and other tumors[59]. These findings are consistent with the results found in other cancers, such as human gliomas, melanoma, and Merkel cell carcinoma, suggesting that aberrant RON expression is also associated with both neurological and skin cancers[18]. In breast tissues, the expression of RON is relatively low in normal breast epithelial cells and even in cells from benign lesions (papilloma and adenoma), whereas its was highly expressed in 47% (35/75 cases) of histologically varied tumor specimens[25]. RON upregulation is associated strongly with its phosphorylation status and invasive activity, suggesting that dysregulated expression of RON functions in human breast carcinoma progression to invasive-metastatic phenotypes. Furthermore, in breast cancer unregulated RON expression was identified as an independent predictor of distant relapse[60]. By contrast, in certain tumors, such as hepatocellular carcinoma (HCC), the frequency of wild-type RON expression was relatively low[21]; however, its importance remains unknown, although this finding indicates that the wild-type RON is not expressed universally in different tumor types. Moreover, RON overexpression is related to oncogenic RON isoform production, for example RON△160, which comprises the deletion of exons 5 and 6, encoding 109 amino acids in the RON β-chain extracellular sequence[12]. RON variants are detected in primary cancer samples and cell lines relatively frequently, and are detected in 40% to 60% of cases. Cancer pathogenesis and clinical relevance are likely to be affected by the frequencies and levels of RON isoforms.

Increasing evidence has demonstrated the role of RON in regulating cancer cell invasiveness, which is related to the effects of RON activation on a variety of signaling mechanisms. The activation of complex downstream signaling networks including signal transducer and activator of transcription, β-catenin, JUN N-terminal kinase, MAPK, and PI3K/AKT pathways are key contributors to RON-mediated aggressive cancer phenotypes. In breast cancer, several signaling pathways that are vital for stemness, invasiveness, and proliferation are activated by RON. For example, the RON-cellular Abelson murine leukemia viral oncogene homolog (c-Abl)-proliferation cell nuclear antigen (PCNA) pathway was identified to contribute to RON-mediated cell growth in breast cancer. Dysregulated RON signaling results in c-Abl activation, consequently leading to PCNA phosphorylation[61]. Moreover, in breast cancer, RON signaling regulates the invasiveness of cancer cell *via* the activation of the DEK proto-oncogene (*DEK*), a DNA-binding non-histone nuclear phosphoprotein that induces closed circular DNA to form positive supercoils[62]. This process appears to function *via* a paracrine and autocrine canonical β-catenin signaling loop, which ultimately influences breast cancer stemness. In addition, RON-mediated PI3K-dependent upregulation of methyl-CpG binding domain 4, DNA glycosylase (MBD4) increases the invasive growth and metastasis of breast cancer cell *via* the reprogramming of the DNA methylation of specific target genes[63]. Clinical data indicated that in patients with breast cancer, poor prognosis is related to the RON-MBD4 epigenetic pathway[63].

**RON RECEPTOR AND HEPATOBILIARY CANCERS**

In 2030, it is estimated that more than 1 million people will die because of liver cancer worldwide[64]. Primary malignancies of the liver and adjacent biliary tract include HCC, intrahepatic and extrahepatic cholangiocarcinoma (CCA), and gallbladder cancer (GBC). Among them, HCC and intrahepatic CCA account for 85% and 10%, respectively[65]. Abnormal RON expression has been observed in HCC, which may be related to pathological conditions of this cancer[43]. In an HCC cell line study, RON was shown to be associated with oncogenic and invasive phenotypes (*e.g.*, resistance to apoptosis, tumor cell migration, and tumor cell invasion) *via* AKT, c-Raf, and extracellular regulated kinase (ERK) signaling cascade modulation[66]. Clinically, RON and MET expression in patients with HCC after curative resection suggested no association of RON with overall survival and overall recurrence rates. However, patients with RON+/MET+ disease experienced higher overall recurrence rates compared with those displaying alternative expression patterns[67]. Similar to HCC, RON is emerging as an important mediator of CCA pathogenesis and clinical prognosis. Investigation of RON and MET expression in patients with perihilar CCA who underwent histologically curative resection revealed that patients with RON+/MET+ disease showed a worse overall survival rate than patients with other patterns[44]. In addition, in patients with extrahepatic CCA, the complete loss of MET, RON, or both (and their overexpression) was a factor for poor prognosis, likely due to the high rate of lymph-node metastasis[68]. Recently, Cheng and co-workers indicated that BMS-777607, a MET-RON dual inhibitor, inhibited HuCCT1 and KKU-100 human CCA cell growth, and decreased the growth of tumors in CCA rats. They further found that for patients with CCA who had previously undergone hepatectomies, upregulation of RON and MET was a predictor of poor survival[69]. Taken together, these studies suggest that the aberrant RON expression found in human hepatobiliary cancer samples and cell lines is closely related to pathological conditions and clinical outcome.

**RON RECEPTOR AND PANCREATIC CANCER**

The majority of malignant neoplasms of the pancreas are adenocarcinomas, among which pancreatic ductal adenocarcinoma is the most common malignancy, representing an excess of 95% of all pancreatic malignancies[70]. Pancreatic cancer presents a substantial health problem and is associated with an extremely poor prognosis because of the non-specific symptoms in patients, its aggressive and remarkable resistance to most conventional treatment options, and the fact that it harbors multiple genetic and epigenetic alterations[42]. Therefore, novel therapies to treat pancreatic cancer are urgently required. In recent years, the function of RON in pancreatic cancer has been identified extensively in a variety of model systems, such as animal, cellular, and clinical settings. To date, researchers have reported that RON is expressed in various pancreatic cancer cell lines, such as CFPAC-1, ASPC-1, Hs766.T, L3.6pl, HPAFⅡ, HPAC, Capan-2, and BXPC-3. However, MIA-PACA-2 cells show minimal RON expression[71]. The association of RON with Kras-driven pancreatic carcinogenesis was investigated using genetically engineered mouse models. The results showed that overexpression of RON accelerated pancreatic intraepithelial neoplasia (PanIN) progression, enhanced acinar-ductal metaplasia, and promoted tumor progression towards invasive pancreatic cancer[72]. Moreover, the study proved that the initiation of PanIN was slowed by RON kinase domain genetic inactivation, resulting in smaller tumors, and eventually prolonging tumor-bearing mouse survival[72]. Great progress has been made in our understanding of the clinical relevance of RON in pancreatic cancer, which has focused mainly on RON expression status in pancreatic cancer samples and its possible utility as a prognostic biomarker for patient survival. IHC staining using anti-RON antibodies is a commonly used approach to evaluate RON expression in various experimental settings. Several studies have identified positive sample rates in pancreatic cancer specimens such as 70%, 88%, 96%, 80%, and 86%, respectively[21,73]. Meanwhile, in pancreatic cancer samples, high RON expression has been detected, whereas minimal levels were detected in their corresponding normal epithelial cells. Notably, during pancreatic cell tumorigenic progression, the frequency and level of RON expression increased[22,74]. Among human pancreatic tissue samples, RON expression was detected in 83% of metastatic lesions, 79% of primary lesions, and 93% of high-grade PanIN using immunohistochemistry, with low expression being detected in low-grade PanIN and normal ducts (18% and 6%, respectively), suggesting that RON might function in pancreatic carcinogenesis and metastatic progression[22]. Moreover, RON expression levels were significantly related to overall survival in patients with pancreatic cancer, indicating that RON could be an important indicator of prognosis in pancreatic cancer[75]. Conflicting results between RON expression and pancreatic cancer prognosis were found in an early study[76], thus more research is needed to determine the utility of RON as a prognostic biomarker in patients with pancreatic cancer.

Primary and metastatic pancreatic tumor specimens and high grade PanIN lesions show increased RON expression[22]. Accumulating evidence suggests that dysregulated RON signaling and activation might function in tumor formation and metastasis. Generally, activation of RON results in increased pancreatic cancer tumorigenic stemness, chemoresistance, survival capability, angiogenesis, and cell invasiveness[73]. Among them, invasiveness occurs *via* a phenotype resembling EMT. A study found that MSP treatment of the pancreatic cancer cell line L3.6pl resulted in increased cell invasion, cell migration, and ERK phosphorylation[24]. Activation of RON resulted in decreased levels of membrane-bound E-cadherin together with β-catenin nuclear translocation, which resembled EMT. Treated L3.6pl cells acquired a spindle shape and lost their polarity, their intercellular separation increased, and more pseudopodia were formed[24]. Aberrant RON activation in collaboration with other growth factors, such as transforming growth factor-β, contributes to the phenotypic changes of pancreatic cancer cells towards EMT. Additionally, an investigation of RON signaling-mediated angiogenesis regulation in pancreatic cancer found that RON signaling leads to MAPK-mediated pancreatic cancer cell production of the well-characterized angiogenic protein, vascular endothelial growth factor. RON activation also caused the promotion of microtubule formation[77]. Finally, the RON signaling pathway also plays a part in chemoresistance, which is associated with enhanced survival capability[51,78]. Short hairpin RNA (shRNA)-mediated silencing of *RON* expression in pancreatic cancer xenografts resulted in increased sensitivity to gemcitabine therapy and susceptibility to apoptosis[51]. In the light of the above findings, it is clear that RON signaling is crucial for pancreatic cancer formation and metastasis.

**RON AS A THERAPEUTIC TARGET FOR HBP CANCERS**

Based on the pathogenic role of RON in cancers, including HBP cancers, efforts have focused predominantly on establishing RON as a drug target for therapeutic intervention[73]. A variety of techniques were proposed to effectively block RON signaling and expression. One approach is to inhibit RON expression using gene silencing with small interfering RNAs (siRNAs). In pancreatic cancer xenografts, *RON* silencing caused growth inhibition by enhancing their apoptosis susceptibility and *via* sensitization to gemcitabine therapy[51]. Thus, delivery of RON-specific siRNAs could have therapeutic potential. In addition, small-molecule kinase inhibitors (SMKIs), which block the receptor tyrosine kinase domain either *via* non-competitive inhibition or *via* ATP competition, have been proposed[45]. The structural similarities between the kinase domains of MET and RON resulted in the development of selective small molecule inhibitors targeting both the RON and MET kinase domains, with slightly different IC50 values. As described above, BMS-777607, a MET-RON dual inhibitor, has shown its effects in inhibiting the growth of human intra-hepatic CCA cell lines and also decreasing tumor growth in intrahepatic CCA rats[69]. However, preclinical studies to prove RON as a drug target showed unsatisfactory results when using RON-specific SMKIs[46,79-81]. The first reason for the above result is that HBP cancer cell survival does not depend on RON signaling. Second, an SMKI that specifically inhibits only RON kinase activities is not available. Synthetic SMKIs, including Tivantinib, BMS-777607, INCB28060, Compound-1, and PHA665752, all recognize both RON and MET, with similar kinase-binding affinities[73]. Thus, the characterized SMKI RON or MET-specific inhibitors are actually multiple RTK inhibitors and the development of SMKIs that exclusively target RON has been a challenge.

A more realistic approach is using anti-RON therapeutic monoclonal antibodies (TPABs) to treat HBP cancers. For instance, anti-RON antibody Zt/c9-directing doxorubicin-immunoliposomes was effective at killing purified pancreatic cancer stem cells *in vitro*. The underlying mechanism is that Zt/c9-directing doxorubicin-immunoliposomes specifically interact with pancreatic cancer stem cells and rapidly cause RON internalization, which leads to the uptake of liposome-coated Dox. In addition, preclinical models have been constructed using anti-RON TPABs, such as 7G8, 6D4, 6E6, narnatumab (or IMC-RON8), Zt/f2, and IMC-41A10, which either block MSP binding by recognizing RON’s ligand-binding pocket or affect receptor dimerization by interacting with RON’s extracellular domain (*e.g.*, SEMA), thereby attenuating signaling transduction[73]. However, previous studies concerning TPAB therapy revealed only partial inhibition of tumor growth, and there have been no reports of single anti-RON TPAB administration achieving complete inhibition. Thus, strategies to maximize anti-RON TPABs’ therapeutic activity have moved on to an exciting new area. Anticancer therapeutic agents comprising antibody-drug conjugates (ADCs) combine the specificity of antibodies with the high potency of cytotoxins to enhance cell killing[12]. To generate RON-targeted ADCs, the anti-RON monoclonal antibodies PCM5B14 and Zt/g4 were selected to prepare immunotoxins. To generate Zt/g4 and PCM5B14-based ADCs, cytotoxic payloads with different mechanisms of action were conjugated, including pyrrolobenzodiazepine, duocarmycin (DCM), monomethyl auristatin E, and maytansinoid derivative 1, forming for example, Zt/g4-MME and PCM5B14-DCM[59]. Preclinical studies identified Zt/g4- and PCM5B14-based ADCs as lead candidates for clinical development and increased the chance of their entering into clinical trials (Table 1).

**CONCLUSION**

RON was identified over two decades ago, and since then, accumulating evidence has indicating RON’s involvement in tumorigenesis, which has resulted in increased momentum for developing RON as a target for therapeutic drug intervention. As outlined in this review, the identification of dysregulated activation and expression of RON in various cancers has expanded our understanding of the mechanisms underlying cancer pathogenesis. Importantly, HBP cancers are characterized pathologically by the dysregulated signaling and expression of RON, which also act as tumorigenic determinants for the malignant behavior of HBP cancers. Moreover, abnormal RON expression is important to determine the clinical outcome of patients with HBP cancers. The growing knowledge concerning the crucial role of RON in HBP cancers can be translated into promising cancer therapeutic strategies. Consequently, a number of clinical trials are underway to assess SMKIs and TPABs targeting RON as a molecular target, some of which have shown promising results. Furthermore, PCM5B14- and Zt/g4-based ADCs, as anti-RON ADCs, are receiving increased research interest and the striking advances in exploiting anti-RON ADCs will hopefully translate into clinical treatments for patients with HBP cancer in the future.

**REFERENCES**

1 **Ronsin C**, Muscatelli F, Mattei MG, Breathnach R. A novel putative receptor protein tyrosine kinase of the met family. *Oncogene* 1993; **8**: 1195-1202 [PMID: 8386824]

2 **Gherardi E**, Sharpe M, Lane K, Sirulnik A, Stoker M. Hepatocyte growth factor/scatter factor (HGF/SF), the c-met receptor and the behaviour of epithelial cells. *Symp Soc Exp Biol* 1993; **47**: 163-181 [PMID: 8165564]

3 **Wagh PK**, Peace BE, Waltz SE. Met-related receptor tyrosine kinase Ron in tumor growth and metastasis. *Adv Cancer Res* 2008; **100**: 1-33 [PMID: 18620091 DOI: 10.1016/S0065-230X(08)00001-8]

4 **Iwama A**, Okano K, Sudo T, Matsuda Y, Suda T. Molecular cloning of a novel receptor tyrosine kinase gene, STK, derived from enriched hematopoietic stem cells. *Blood* 1994; **83**: 3160-3169 [PMID: 8193352]

5 **De Maria R**, Maggiora P, Biolatti B, Prat M, Comoglio PM, Castagnaro M, Di Renzo MF. Feline STK gene expression in mammary carcinomas. *Oncogene* 2002; **21**: 1785-1790 [PMID: 11896610 DOI: 10.1038/sj.onc.1205221]

6 **Bassett DI**. Identification and developmental expression of a macrophage stimulating 1/ hepatocyte growth factor-like 1 orthologue in the zebrafish. *Dev Genes Evol* 2003; **213**: 360-362 [PMID: 12764615 DOI: 10.1007/s00427-003-0339-3]

7 **Huitema LF**, Renn J, Logister I, Gray JK, Waltz SE, Flik G, Schulte-Merker S. Macrophage-stimulating protein and calcium homeostasis in zebrafish. *FASEB J* 2012; **26**: 4092-4101 [PMID: 22787265 DOI: 10.1096/fj.11-202663]

8 **Théry C**, Sharpe MJ, Batley SJ, Stern CD, Gherardi E. Expression of HGF/SF, HGF1/MSP, and c-met suggests new functions during early chick development. *Dev Genet* 1995; **17**: 90-101 [PMID: 7554499 DOI: 10.1002/dvg.1020170110]

9 **Huff JL**, Jelinek MA, Jamieson TA, Parsons JT. Expression and maturation of the cellular sea receptor, a member of the hepatocyte growth factor (HGF) receptor family of protein tyrosine kinases. *Oncogene* 1996; **12**: 299-307 [PMID: 8570207]

10 **Wahl RC**, Hsu RY, Huff JL, Jelinek MA, Chen K, Courchesne P, Patterson SD, Parsons JT, Welcher AA. Chicken macrophage stimulating protein is a ligand of the receptor protein-tyrosine kinase Sea. *J Biol Chem* 1999; **274**: 26361-26368 [PMID: 10473593 DOI: 10.1074/jbc.274.37.26361]

11 **Nakamura T**, Aoki S, Takahashi T, Matsumoto K, Kiyohara T, Nakamura T. Cloning and expression of Xenopus HGF-like protein (HLP) and Ron/HLP receptor implicate their involvement in early neural development. *Biochem Biophys Res Commun* 1996; **224**: 564-573 [PMID: 8702427 DOI: 10.1006/bbrc.1996.1065]

12 **Yao HP**, Zhou YQ, Zhang R, Wang MH. MSP-RON signalling in cancer: pathogenesis and therapeutic potential. *Nat Rev Cancer* 2013; **13**: 466-481 [PMID: 23792360 DOI: 10.1038/nrc3545]

13 **Wang MH**, Iwama A, Skeel A, Suda T, Leonard EJ. The murine stk gene product, a transmembrane protein tyrosine kinase, is a receptor for macrophage-stimulating protein. *Proc Natl Acad Sci U S A* 1995; **92**: 3933-3937 [PMID: 7732008 DOI: 10.1073/pnas.92.9.3933]

14 **Wang MH**, Ronsin C, Gesnel MC, Coupey L, Skeel A, Leonard EJ, Breathnach R. Identification of the ron gene product as the receptor for the human macrophage stimulating protein. *Science* 1994; **266**: 117-119 [PMID: 7939629 DOI: 10.1126/science.7939629]

15 **Gaudino G**, Follenzi A, Naldini L, Collesi C, Santoro M, Gallo KA, Godowski PJ, Comoglio PM. RON is a heterodimeric tyrosine kinase receptor activated by the HGF homologue MSP. *EMBO J* 1994; **13**: 3524-3532 [PMID: 8062829]

16 **Han S**, Stuart LA, Degen SJ. Characterization of the DNF15S2 Locus on human chromosome 3: identification of a gene coding for four kringle domains with homology to hepatocyte growth factor. *Biochemistry* 1991; **30**: 9768-9780 [PMID: 1655021 DOI: 10.1021/bi00104a029]

17 **Yoshimura T**, Yuhki N, Wang MH, Skeel A, Leonard EJ. Cloning, sequencing, and expression of human macrophage stimulating protein (MSP, MST1) confirms MSP as a member of the family of kringle proteins and locates the MSP gene on chromosome 3. *J Biol Chem* 1993; **268**: 15461-15468 [PMID: 8393443]

18 **Benight NM**, Waltz SE. Ron receptor tyrosine kinase signaling as a therapeutic target. *Expert Opin Ther Targets* 2012; **16**: 921-931 [PMID: 22834780 DOI: 10.1517/14728222.2012.710200]

19 **Wang MH**, Julian FM, Breathnach R, Godowski PJ, Takehara T, Yoshikawa W, Hagiya M, Leonard EJ. Macrophage stimulating protein (MSP) binds to its receptor *via* the MSP beta chain. *J Biol Chem* 1997; **272**: 16999-17004 [PMID: 9202013 DOI: 10.1074/jbc.272.27.16999]

20 **Danilkovitch A**, Miller M, Leonard EJ. Interaction of macrophage-stimulating protein with its receptor. Residues critical for beta chain binding and evidence for independent alpha chain binding. *J Biol Chem* 1999; **274**: 29937-29943 [PMID: 10514476 DOI: 10.1074/jbc.274.42.29937]

21 **Wang MH**, Lee W, Luo YL, Weis MT, Yao HP. Altered expression of the RON receptor tyrosine kinase in various epithelial cancers and its contribution to tumourigenic phenotypes in thyroid cancer cells. *J Pathol* 2007; **213**: 402-411 [PMID: 17955509 DOI: 10.1002/path.2245]

22 **Thomas RM**, Toney K, Fenoglio-Preiser C, Revelo-Penafiel MP, Hingorani SR, Tuveson DA, Waltz SE, Lowy AM. The RON receptor tyrosine kinase mediates oncogenic phenotypes in pancreatic cancer cells and is increasingly expressed during pancreatic cancer progression. *Cancer Res* 2007; **67**: 6075-6082 [PMID: 17616662 DOI: 10.1158/0008-5472.CAN-06-4128]

23 **Kanteti R**, Krishnaswamy S, Catenacci D, Tan YH, EL-Hashani E, Cervantes G, Husain AN, Tretiakova M, Vokes EE, Huet H, Salgia R. Differential expression of RON in small and non-small cell lung cancers. *Genes Chromosomes Cancer* 2012; **51**: 841-851 [PMID: 22585712 DOI: 10.1002/gcc.21968]

24 **Camp ER**, Yang A, Gray MJ, Fan F, Hamilton SR, Evans DB, Hooper AT, Pereira DS, Hicklin DJ, Ellis LM. Tyrosine kinase receptor RON in human pancreatic cancer: expression, function, and validation as a target. *Cancer* 2007; **109**: 1030-1039 [PMID: 17311308 DOI: 10.1002/cncr.22490]

25 **Maggiora P**, Marchio S, Stella MC, Giai M, Belfiore A, De Bortoli M, Di Renzo MF, Costantino A, Sismondi P, Comoglio PM. Overexpression of the RON gene in human breast carcinoma. *Oncogene* 1998; **16**: 2927-2933 [PMID: 9671413 DOI: 10.1038/sj.onc.1201812]

26 **Catenacci DV**, Cervantes G, Yala S, Nelson EA, El-Hashani E, Kanteti R, El Dinali M, Hasina R, Brägelmann J, Seiwert T, Sanicola M, Henderson L, Grushko TA, Olopade O, Karrison T, Bang YJ, Kim WH, Tretiakova M, Vokes E, Frank DA, Kindler HL, Huet H, Salgia R. RON (MST1R) is a novel prognostic marker and therapeutic target for gastroesophageal adenocarcinoma. *Cancer Biol Ther* 2011; **12**: 9-46 [PMID: 21543897 DOI: 10.4161/cbt.12.1.15747]

27 **Ren X**, Daa T, Yada N, Kashima K, Fujitomi Y, Yokoyama S. Expression and mutational status of RON in neoplastic lesions of the breast: analysis of MSP/RON signaling in ductal carcinoma in situ and invasive ductal carcinoma. *APMIS* 2012; **120**: 358-367 [PMID: 22515290 DOI: 10.1111/j.1600-0463.2011.02841.x]

28 **Chou YC**, Chen CL, Yeh TH, Lin SJ, Chen MR, Doong SL, Lu J, Tsai CH. Involvement of recepteur d'origine nantais receptor tyrosine kinase in Epstein-Barr virus-associated nasopharyngeal carcinoma and its metastasis. *Am J Pathol* 2012; **181**: 1773-1781 [PMID: 22974584 DOI: 10.1016/j.ajpath.2012.07.014]

29 **Collesi C**, Santoro MM, Gaudino G, Comoglio PM. A splicing variant of the RON transcript induces constitutive tyrosine kinase activity and an invasive phenotype. *Mol Cell Biol* 1996; **16**: 5518-5526 [PMID: 8816464 DOI: 10.1128/mcb.16.10.5518]

30 **Santoro MM**, Collesi C, Grisendi S, Gaudino G, Comoglio PM. Constitutive activation of the RON gene promotes invasive growth but not transformation. *Mol Cell Biol* 1996; **16**: 7072-7083 [PMID: 8943362 DOI: 10.1128/mcb.16.12.7072]

31 **Zhou YQ**, He C, Chen YQ, Wang D, Wang MH. Altered expression of the RON receptor tyrosine kinase in primary human colorectal adenocarcinomas: generation of different splicing RON variants and their oncogenic potential. *Oncogene* 2003; **22**: 186-197 [PMID: 12527888 DOI: 10.1038/sj.onc.1206075]

32 **Liu X**, Zhao L, Derose YS, Lin YC, Bieniasz M, Eyob H, Buys SS, Neumayer L, Welm AL. Short-Form Ron Promotes Spontaneous Breast Cancer Metastasis through Interaction with Phosphoinositide 3-Kinase. *Genes Cancer* 2011; **2**: 753-762 [PMID: 22207901 DOI: 10.1177/1947601911421924]

33 **Eckerich C**, Schulte A, Martens T, Zapf S, Westphal M, Lamszus K. RON receptor tyrosine kinase in human gliomas: expression, function, and identification of a novel soluble splice variant. *J Neurochem* 2009; **109**: 969-980 [PMID: 19519771 DOI: 10.1111/j.1471-4159.2009.06027.x]

34 **Ma Q**, Zhang K, Guin S, Zhou YQ, Wang MH. Deletion or insertion in the first immunoglobulin-plexin-transcription (IPT) domain differentially regulates expression and tumorigenic activities of RON receptor Tyrosine Kinase. *Mol Cancer* 2010; **9**: 307 [PMID: 21114864 DOI: 10.1186/1476-4598-9-307]

35 **Wei X**, Hao L, Ni S, Liu Q, Xu J, Correll PH. Altered exon usage in the juxtamembrane domain of mouse and human RON regulates receptor activity and signaling specificity. *J Biol Chem* 2005; **280**: 40241-40251 [PMID: 16166096 DOI: 10.1074/jbc.M506806200]

36 **Ghigna C**, Giordano S, Shen H, Benvenuto F, Castiglioni F, Comoglio PM, Green MR, Riva S, Biamonti G. Cell motility is controlled by SF2/ASF through alternative splicing of the Ron protooncogene. *Mol Cell* 2005; **20**: 881-890 [PMID: 16364913 DOI: 10.1016/j.molcel.2005.10.026]

37 **Fialin C**, Larrue C, Vergez F, Sarry JE, Bertoli S, Mansat-De Mas V, Demur C, Delabesse E, Payrastre B, Manenti S, Roche S, Récher C. The short form of RON is expressed in acute myeloid leukemia and sensitizes leukemic cells to cMET inhibitors. *Leukemia* 2013; **27**: 325-335 [PMID: 22902361 DOI: 10.1038/leu.2012.240]

38 **Bardella C**, Costa B, Maggiora P, Patane' S, Olivero M, Ranzani GN, De Bortoli M, Comoglio PM, Di Renzo MF. Truncated RON tyrosine kinase drives tumor cell progression and abrogates cell-cell adhesion through E-cadherin transcriptional repression. *Cancer Res* 2004; **64**: 5154-5161 [PMID: 15289319 DOI: 10.1158/0008-5472.CAN-04-0600]

39 **Wang MH**, Kurtz AL, Chen Y. Identification of a novel splicing product of the RON receptor tyrosine kinase in human colorectal carcinoma cells. *Carcinogenesis* 2000; **21**: 1507-1512 [PMID: 10910951]

40 **Wu LM**, Zhang LL, Chen XH, Zheng SS. Is irreversible electroporation safe and effective in the treatment of hepatobiliary and pancreatic cancers? *Hepatobiliary Pancreat Dis Int* 2019; **18**: 117-124 [PMID: 30655073 DOI: 10.1016/j.hbpd.2019.01.001]

41 **Ueno M**, Morizane C, Ikeda M, Okusaka T, Ishii H, Furuse J. A review of changes to and clinical implications of the eighth TNM classification of hepatobiliary and pancreatic cancers. *Jpn J Clin Oncol* 2019; **49**: 1073-1082 [PMID: 31822900 DOI: 10.1093/jjco/hyz150]

42 **Kleeff J**, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, Neale RE, Tempero M, Tuveson DA, Hruban RH, Neoptolemos JP. Pancreatic cancer. *Nat Rev Dis Primers* 2016; **2**: 16022 [PMID: 27158978 DOI: 10.1038/nrdp.2016.22]

43 **Chen Q**, Seol DW, Carr B, Zarnegar R. Co-expression and regulation of Met and Ron proto-oncogenes in human hepatocellular carcinoma tissues and cell lines. *Hepatology* 1997; **26**: 59-66 [PMID: 9214452 DOI: 10.1002/hep.510260108]

44 **Watanabe H**, Yokoyama Y, Kokuryo T, Ebata T, Igami T, Sugawara G, Mizuno T, Shimoyama Y, Nagino M. Prognostic Value of Hepatocyte Growth Factor Receptor Expression in Patients with Perihilar Cholangiocarcinoma. *Ann Surg Oncol* 2015; **22**: 2235-2242 [PMID: 25586241 DOI: 10.1245/s10434-014-4170-z]

45 **Wang MH**, Padhye SS, Guin S, Ma Q, Zhou YQ. Potential therapeutics specific to c-MET/RON receptor tyrosine kinases for molecular targeting in cancer therapy. *Acta Pharmacol Sin* 2010; **31**: 1181-1188 [PMID: 20694025 DOI: 10.1038/aps.2010.106]

46 **Dussault I**, Bellon SF. From concept to reality: the long road to c-Met and RON receptor tyrosine kinase inhibitors for the treatment of cancer. *Anticancer Agents Med Chem* 2009; **9**: 221-229 [PMID: 19199866 DOI: 10.2174/187152009787313792]

47 **Chang K**, Karnad A, Zhao S, Freeman JW. Roles of c-Met and RON kinases in tumor progression and their potential as therapeutic targets. *Oncotarget* 2015; **6**: 3507-3518 [PMID: 25784650 DOI: 10.18632/oncotarget.3420]

48 **Lee CT**, Chow NH, Su PF, Lin SC, Lin PC, Lee JC. The prognostic significance of RON and MET receptor coexpression in patients with colorectal cancer. *Dis Colon Rectum* 2008; **51**: 1268-1274 [PMID: 18536971 DOI: 10.1007/s10350-008-9297-1]

49 **Ponzo MG**, Lesurf R, Petkiewicz S, O'Malley FP, Pinnaduwage D, Andrulis IL, Bull SB, Chughtai N, Zuo D, Souleimanova M, Germain D, Omeroglu A, Cardiff RD, Hallett M, Park M. Met induces mammary tumors with diverse histologies and is associated with poor outcome and human basal breast cancer. *Proc Natl Acad Sci U S A* 2009; **106**: 12903-12908 [PMID: 19617568 DOI: 10.1073/pnas.0810402106]

50 **Comoglio PM**, Trusolino L, Boccaccio C. Known and novel roles of the MET oncogene in cancer: a coherent approach to targeted therapy. *Nat Rev Cancer* 2018; **18**: 341-358 [PMID: 29674709 DOI: 10.1038/s41568-018-0002-y]

51 **Logan-Collins J**, Thomas RM, Yu P, Jaquish D, Mose E, French R, Stuart W, McClaine R, Aronow B, Hoffman RM, Waltz SE, Lowy AM. Silencing of RON receptor signaling promotes apoptosis and gemcitabine sensitivity in pancreatic cancers. *Cancer Res* 2010; **70**: 1130-1140 [PMID: 20103639 DOI: 10.1158/0008-5472.CAN-09-0761]

52 **Zarei O**, Benvenuti S, Ustun-Alkan F, Hamzeh-Mivehroud M, Dastmalchi S. Strategies of targeting the extracellular domain of RON tyrosine kinase receptor for cancer therapy and drug delivery. *J Cancer Res Clin Oncol* 2016; **142**: 2429-2446 [PMID: 27503093 DOI: 10.1007/s00432-016-2214-4]

53 **Wang X**, Hankey PA. The ron receptor tyrosine kinase: a key regulator of inflammation and cancer progression. *Crit Rev Immunol* 2013; **33**: 549-574 [PMID: 24266348 DOI: 10.1615/critrevimmunol.2013007953]

54 **Xiao ZQ**, Chen YQ, Wang MH. Requirement of both tyrosine residues 1330 and 1337 in the C-terminal tail of the RON receptor tyrosine kinase for epithelial cell scattering and migration. *Biochem Biophys Res Commun* 2000; **267**: 669-675 [PMID: 10631120 DOI: 10.1006/bbrc.1999.2011]

55 **Wang J**, Rajput A, Kan JL, Rose R, Liu XQ, Kuropatwinski K, Hauser J, Beko A, Dominquez I, Sharratt EA, Brattain L, Levea C, Sun FL, Keane DM, Gibson NW, Brattain MG. Knockdown of Ron kinase inhibits mutant phosphatidylinositol 3-kinase and reduces metastasis in human colon carcinoma. *J Biol Chem* 2009; **284**: 10912-10922 [PMID: 19224914 DOI: 10.1074/jbc.M809551200]

56 **Wang D**, Shen Q, Chen YQ, Wang MH. Collaborative activities of macrophage-stimulating protein and transforming growth factor-beta1 in induction of epithelial to mesenchymal transition: roles of the RON receptor tyrosine kinase. *Oncogene* 2004; **23**: 1668-1680 [PMID: 15001985 DOI: 10.1038/sj.onc.1207282]

57 **Ma Q**, Guin S, Padhye SS, Zhou YQ, Zhang RW, Wang MH. Ribosomal protein S6 kinase (RSK)-2 as a central effector molecule in RON receptor tyrosine kinase mediated epithelial to mesenchymal transition induced by macrophage-stimulating protein. *Mol Cancer* 2011; **10**: 66 [PMID: 21619683 DOI: 10.1186/1476-4598-10-66]

58 **Faham N**, Welm AL. RON Signaling Is a Key Mediator of Tumor Progression in Many Human Cancers. *Cold Spring Harb Symp Quant Biol* 2016; **81**: 177-188 [PMID: 28057847 DOI: 10.1101/sqb.2016.81.031377]

59 **Yao HP**, Suthe SR, Tong XM, Wang MH. Targeting RON receptor tyrosine kinase for treatment of advanced solid cancers: antibody-drug conjugates as lead drug candidates for clinical trials. *Ther Adv Med Oncol* 2020; **12**: 1758835920920069 [PMID: 32426050 DOI: 10.1177/1758835920920069]

60 **Lee WY**, Chen HH, Chow NH, Su WC, Lin PW, Guo HR. Prognostic significance of co-expression of RON and MET receptors in node-negative breast cancer patients. *Clin Cancer Res* 2005; **11**: 2222-2228 [PMID: 15788670 DOI: 10.1158/1078-0432.CCR-04-1761]

61 **Zhao H**, Chen MS, Lo YH, Waltz SE, Wang J, Ho PC, Vasiliauskas J, Plattner R, Wang YL, Wang SC. The Ron receptor tyrosine kinase activates c-Abl to promote cell proliferation through tyrosine phosphorylation of PCNA in breast cancer. *Oncogene* 2014; **33**: 1429-1437 [PMID: 23542172 DOI: 10.1038/onc.2013.84]

62 **Privette Vinnedge LM**, Benight NM, Wagh PK, Pease NA, Nashu MA, Serrano-Lopez J, Adams AK, Cancelas JA, Waltz SE, Wells SI. The DEK oncogene promotes cellular proliferation through paracrine Wnt signaling in Ron receptor-positive breast cancers. *Oncogene* 2015; **34**: 2325-2336 [PMID: 24954505 DOI: 10.1038/onc.2014.173]

63 **Bellacosa A**. Role of MED1 (MBD4) Gene in DNA repair and human cancer. *J Cell Physiol* 2001; **187**: 137-144 [PMID: 11267993 DOI: 10.1002/jcp.1064]

64 **Villanueva A**. Hepatocellular Carcinoma. *N Engl J Med* 2019; **380**: 1450-1462 [PMID: 30970190 DOI: 10.1056/NEJMra1713263]

65 **Nault JC**, Villanueva A. Biomarkers for Hepatobiliary Cancers. *Hepatology* 2021; **73 Suppl 1**: 115-127 [PMID: 32045030 DOI: 10.1002/hep.31175]

66 **Cho SB**, Park YL, Song YA, Kim KY, Lee GH, Cho DH, Myung DS, Park KJ, Lee WS, Chung IJ, Choi SK, Kim KK, Joo YE. Small interfering RNA-directed targeting of RON alters invasive and oncogenic phenotypes of human hepatocellular carcinoma cells. *Oncol Rep* 2011; **26**: 1581-1586 [PMID: 21874262 DOI: 10.3892/or.2011.1435]

67 **Koh YW**, Park YS, Kang HJ, Shim JH, Yu E. MET is a predictive factor for late recurrence but not for overall survival of early stage hepatocellular carcinoma. *Tumour Biol* 2015; **36**: 4993-5000 [PMID: 25874493 DOI: 10.1007/s13277-015-3150-7]

68 **Hayashi Y**, Yamaguchi J, Kokuryo T, Ebata T, Yokoyama Y, Igami T, Sugawara G, Nagino M. The Complete Loss of Tyrosine Kinase Receptors MET and RON Is a Poor Prognostic Factor in Patients with Extrahepatic Cholangiocarcinoma. *Anticancer Res* 2016; **36**: 6585-6592 [PMID: 27919987 DOI: 10.21873/anticanres.11263]

69 **Cheng CT**, Chen YY, Wu RC, Tsai CY, Chiang KC, Yeh TS, Chen MH, Yeh CN. MET‑RON dual inhibitor, BMS‑777607, suppresses cholangiocarcinoma cell growth, and MET‑RON upregulation indicates worse prognosis for intra‑hepatic cholangiocarcinoma patients. *Oncol Rep* 2018; **40**: 1411-1421 [PMID: 30015968 DOI: 10.3892/or.2018.6543]

70 **Collisson EA**, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 207-220 [PMID: 30718832 DOI: 10.1038/s41575-019-0109-y]

71 **Kang CM**, Babicky ML, Lowy AM. The RON receptor tyrosine kinase in pancreatic cancer pathogenesis and its potential implications for future targeted therapies. *Pancreas* 2014; **43**: 183-189 [PMID: 24518495 DOI: 10.1097/MPA.0000000000000088]

72 **Babicky ML**, Harper MM, Chakedis J, Cazes A, Mose ES, Jaquish DV, French RP, Childers B, Alakus H, Schmid MC, Foubert P, Miyamoto J, Holman PJ, Walterscheid ZJ, Tang CM, Varki N, Sicklick JK, Messer K, Varner JA, Waltz SE, Lowy AM. MST1R kinase accelerates pancreatic cancer progression *via* effects on both epithelial cells and macrophages. *Oncogene* 2019; **38**: 5599-5611 [PMID: 30967626 DOI: 10.1038/s41388-019-0811-9]

73 **Yao HP**, Hudson R, Wang MH. RON receptor tyrosine kinase in pancreatic ductal adenocarcinoma: Pathogenic mechanism in malignancy and pharmaceutical target for therapy. *Biochim Biophys Acta Rev Cancer* 2020; **1873**: 188360 [PMID: 32234337 DOI: 10.1016/j.bbcan.2020.188360]

74 **Li C**, Morvaridi S, Lam G, Chheda C, Kamata Y, Katsumata M, Edderkaoui M, Yuan X, Nissen N, Pandol SJ, Wang Q. MSP-RON Signaling Is Activated in the Transition From Pancreatic Intraepithelial Neoplasia (PanIN) to Pancreatic Ductal Adenocarcinoma (PDAC). *Front Physiol* 2019; **10**: 147 [PMID: 30863319 DOI: 10.3389/fphys.2019.00147]

75 **Hu CY**, Xu XM, Hong B, Wu ZG, Qian Y, Weng TH, Liu YZ, Tang TM, Wang MH, Yao HP. Aberrant RON and MET Co-overexpression as Novel Prognostic Biomarkers of Shortened Patient Survival and Therapeutic Targets of Tyrosine Kinase Inhibitors in Pancreatic Cancer. *Front Oncol* 2019; **9**: 1377 [PMID: 31867280 DOI: 10.3389/fonc.2019.01377]

76 **Tactacan CM**, Chang DK, Cowley MJ, Humphrey ES, Wu J, Gill AJ, Chou A, Nones K, Grimmond SM, Sutherland RL, Biankin AV, Daly RJ; Australian Pancreratic Genome Initiative. RON is not a prognostic marker for resectable pancreatic cancer. *BMC Cancer* 2012; **12**: 395 [PMID: 22958871 DOI: 10.1186/1471-2407-12-395]

77 **Thomas RM**, Jaquish DV, French RP, Lowy AM. The RON tyrosine kinase receptor regulates vascular endothelial growth factor production in pancreatic cancer cells. *Pancreas* 2010; **39**: 301-307 [PMID: 20358644 DOI: 10.1097/mpa.0b013e3181bb9f73]

78 **Zou Y**, Howell GM, Humphrey LE, Wang J, Brattain MG. Ron knockdown and Ron monoclonal antibody IMC-RON8 sensitize pancreatic cancer to histone deacetylase inhibitors (HDACi). *PLoS One* 2013; **8**: e69992 [PMID: 23922886 DOI: 10.1371/journal.pone.0069992]

79 **Kawada I**, Hasina R, Arif Q, Mueller J, Smithberger E, Husain AN, Vokes EE, Salgia R. Dramatic antitumor effects of the dual MET/RON small-molecule inhibitor LY2801653 in non-small cell lung cancer. *Cancer Res* 2014; **74**: 884-895 [PMID: 24305878 DOI: 10.1158/0008-5472.CAN-12-3583]

80 **Christensen JG**, Schreck R, Burrows J, Kuruganti P, Chan E, Le P, Chen J, Wang X, Ruslim L, Blake R, Lipson KE, Ramphal J, Do S, Cui JJ, Cherrington JM, Mendel DB. A selective small molecule inhibitor of c-Met kinase inhibits c-Met-dependent phenotypes *in vitro* and exhibits cytoreductive antitumor activity in vivo. *Cancer Res* 2003; **63**: 7345-7355 [PMID: 14612533]

81 **Liu X**, Wang Q, Yang G, Marando C, Koblish HK, Hall LM, Fridman JS, Behshad E, Wynn R, Li Y, Boer J, Diamond S, He C, Xu M, Zhuo J, Yao W, Newton RC, Scherle PA. A novel kinase inhibitor, INCB28060, blocks c-MET-dependent signaling, neoplastic activities, and cross-talk with EGFR and HER-3. *Clin Cancer Res* 2011; **17**: 7127-7138 [PMID: 21918175 DOI: 10.1158/1078-0432.CCR-11-1157]

82 **Eder JP**, Shapiro GI, Appleman LJ, Zhu AX, Miles D, Keer H, Cancilla B, Chu F, Hitchcock-Bryan S, Sherman L, McCallum S, Heath EI, Boerner SA, LoRusso PM. A phase I study of foretinib, a multi-targeted inhibitor of c-Met and vascular endothelial growth factor receptor 2. *Clin Cancer Res* 2010; **16**: 3507-3516 [PMID: 20472683 DOI: 10.1158/1078-0432.CCR-10-0574]

83 **Belalcazar A**, Azaña D, Perez CA, Raez LE, Santos ES. Targeting the Met pathway in lung cancer. *Expert Rev Anticancer Ther* 2012; **12**: 519-528 [PMID: 22500688 DOI: 10.1586/era.12.16]

84 **Sharma S**, Zeng JY, Zhuang CM, Zhou YQ, Yao HP, Hu X, Zhang R, Wang MH. Small-molecule inhibitor BMS-777607 induces breast cancer cell polyploidy with increased resistance to cytotoxic chemotherapy agents. *Mol Cancer Ther* 2013; **12**: 725-736 [PMID: 23468529 DOI: 10.1158/1535-7163.MCT-12-1079]

85 **Pan BS**, Chan GK, Chenard M, Chi A, Davis LJ, Deshmukh SV, Gibbs JB, Gil S, Hang G, Hatch H, Jewell JP, Kariv I, Katz JD, Kunii K, Lu W, Lutterbach BA, Paweletz CP, Qu X, Reilly JF, Szewczak AA, Zeng Q, Kohl NE, Dinsmore CJ. MK-2461, a novel multitargeted kinase inhibitor, preferentially inhibits the activated c-Met receptor. *Cancer Res* 2010; **70**: 1524-1533 [PMID: 20145145 DOI: 10.1158/0008-5472.CAN-09-2541]

86 **Northrup AB**, Katcher MH, Altman MD, Chenard M, Daniels MH, Deshmukh SV, Falcone D, Guerin DJ, Hatch H, Li C, Lu W, Lutterbach B, Allison TJ, Patel SB, Reilly JF, Reutershan M, Rickert KW, Rosenstein C, Soisson SM, Szewczak AA, Walker D, Wilson K, Young JR, Pan BS, Dinsmore CJ. Discovery of 1-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]-N-(pyridin-2-ylmethyl)methanesulfonamide (MK-8033): A Specific c-Met/Ron dual kinase inhibitor with preferential affinity for the activated state of c-Met. *J Med Chem* 2013; **56**: 2294-2310 [PMID: 23379595 DOI: 10.1021/jm301619u]

87 **Comoglio PM**, Giordano S, Trusolino L. Drug development of MET inhibitors: targeting oncogene addiction and expedience. *Nat Rev Drug Discov* 2008; **7**: 504-516 [PMID: 18511928 DOI: 10.1038/nrd2530]

88 **Qin S**, Chan SL, Sukeepaisarnjaroen W, Han G, Choo SP, Sriuranpong V, Pan H, Yau T, Guo Y, Chen M, Ren Z, Xu J, Yen CJ, Lin ZZ, Manenti L, Gu Y, Sun Y, Tiedt R, Hao L, Song W, Tanwandee T. A phase II study of the efficacy and safety of the MET inhibitor capmatinib (INC280) in patients with advanced hepatocellular carcinoma. *Ther Adv Med Oncol* 2019; **11**: 1758835919889001 [PMID: 31853265 DOI: 10.1177/1758835919889001]

89 **Rimassa L**, Assenat E, Peck-Radosavljevic M, Pracht M, Zagonel V, Mathurin P, Rota Caremoli E, Porta C, Daniele B, Bolondi L, Mazzaferro V, Harris W, Damjanov N, Pastorelli D, Reig M, Knox J, Negri F, Trojan J, López López C, Personeni N, Decaens T, Dupuy M, Sieghart W, Abbadessa G, Schwartz B, Lamar M, Goldberg T, Shuster D, Santoro A, Bruix J. Tivantinib for second-line treatment of MET-high, advanced hepatocellular carcinoma (METIV-HCC): a final analysis of a phase 3, randomised, placebo-controlled study. *Lancet Oncol* 2018; **19**: 682-693 [PMID: 29625879 DOI: 10.1016/S1470-2045(18)30146-3]

90 **Guin S**, Ma Q, Padhye S, Zhou YQ, Yao HP, Wang MH. Targeting acute hypoxic cancer cells by doxorubicin-immunoliposomes directed by monoclonal antibodies specific to RON receptor tyrosine kinase. *Cancer Chemother Pharmacol* 2011; **67**: 1073-1083 [PMID: 20658288 DOI: 10.1007/s00280-010-1408-8]

91 **Feng L**, Yao HP, Wang W, Zhou YQ, Zhou J, Zhang R, Wang MH. Efficacy of anti-RON antibody Zt/g4-drug maytansinoid conjugation (Anti-RON ADC) as a novel therapeutics for targeted colorectal cancer therapy. *Clin Cancer Res* 2014; **20**: 6045-6058 [PMID: 25294907 DOI: 10.1158/1078-0432.CCR-14-0898]

92 **Yao HP**, Feng L, Suthe SR, Chen LH, Weng TH, Hu CY, Jun ES, Wu ZG, Wang WL, Kim SC, Tong XM, Wang MH. Therapeutic efficacy, pharmacokinetic profiles, and toxicological activities of humanized antibody-drug conjugate Zt/g4-MMAE targeting RON receptor tyrosine kinase for cancer therapy. *J Immunother Cancer* 2019; **7**: 75 [PMID: 30871619 DOI: 10.1186/s40425-019-0525-0]

93 **Yang CY**, Wang L, Sun X, Tang M, Quan HT, Zhang LS, Lou LG, Gou SH. SHR-A1403, a novel c-Met antibody-drug conjugate, exerts encouraging anti-tumor activity in c-Met-overexpressing models. *Acta Pharmacol Sin* 2019; **40**: 971-979 [PMID: 30643210 DOI: 10.1038/s41401-018-0198-0]

**Footnotes**

**Conflict-of-interest statement:** No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** December 31, 2020

**First decision:** February 23, 2021

**Article in press:** April 9, 2021

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

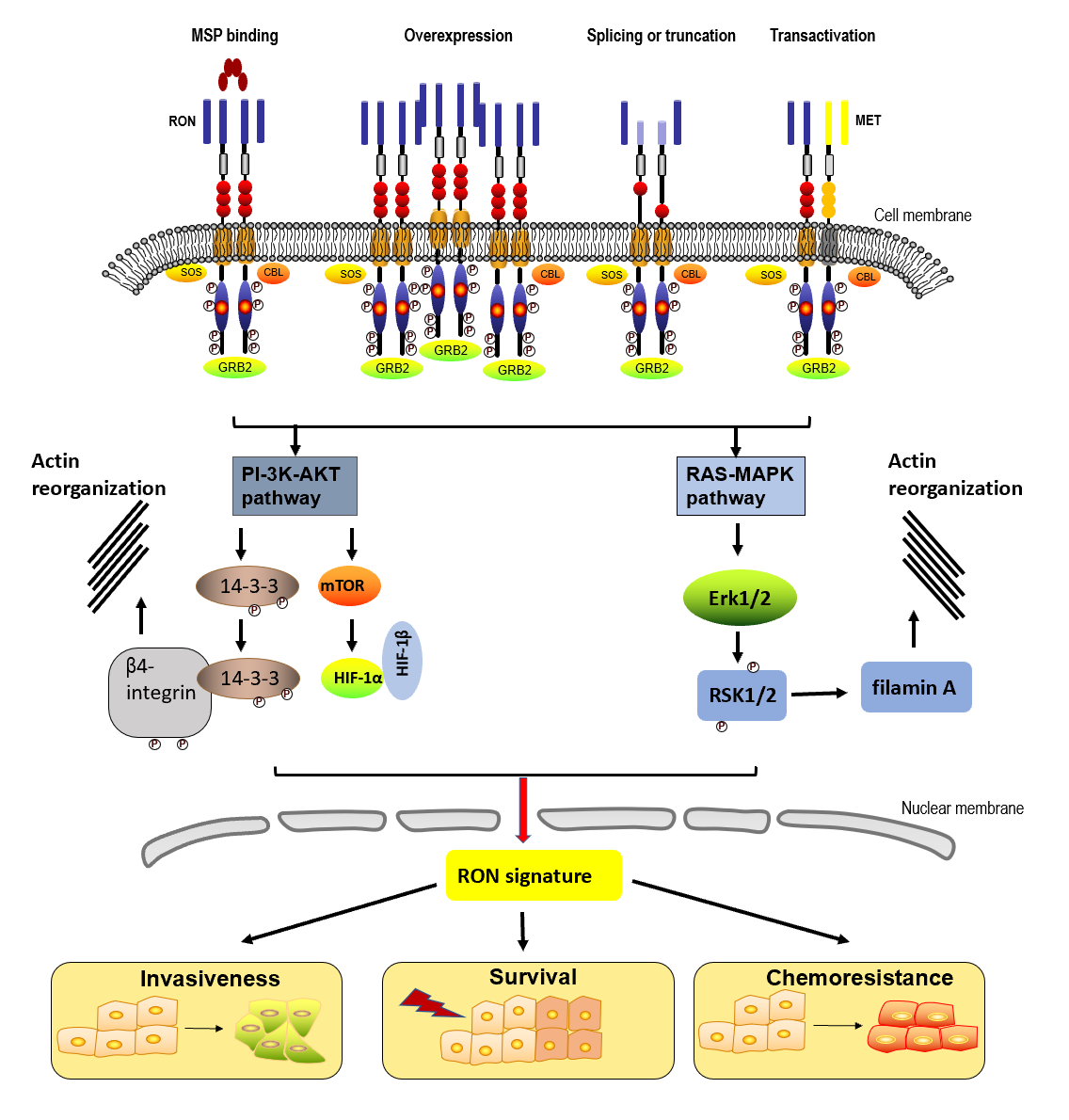
Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Gomes A, Tangkawattana S **S-Editor:** Gao CC **L-Editor:** Wang TQ **P-Editor:** Liu JH

**Figure Legends**



**Figure 1 Mechanisms of RON activation and downstream signaling pathways.** Classically, macrophage-stimulating protein (MSP) activates RON. In cancer, RON activation is induced by overexpression, splicing or truncation, and transactivation. The RON receptor consists of three regions including the extracellular domain, the transmembrane domain, as well as the intracellular domain. MSP binding to the extracellular domain leads to autophosphorylation of several tyrosine residues in the kinase activation loop or in the C-terminal tail, resulting in the activation of many biological activities, including increased proliferation/survival, motile-invasive activity, and chemoresistance. MSP: Macrophage-stimulating protein; SOS: Son of Sevenless; GRB2: Growth factor receptor-bound protein 2; CBL: Casitas B-lineage lymphoma; 14-3-3: Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein; PI-3K-AKT: Phosphatidylinositol-4,5-Bisphosphate 3 kinase- protein kinase B; HIF: Hypoxia-inducible factor; RAS-MAPK: RAS-mitogen-activated protein kinase; ERK: Extracellular regulated kinase; RSK: Ribosomal protein S6 kinase; mTOR: Mechanistic target of rapamycin.

**Table 1 Tyrosine kinase inhibitors and antibody drug conjugates specific to c-MET and RON**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Therapeutic agents** | **Manufacturer** | **Target** | ***In vitro* effects** | **Effects in animal tumor models** | **Clinical trial information** | **Status** | **Ref.** |
| TKIs |  |  |  |  |  |  |  |
| Foretinib | GlaxoSmithKline | MET, RON, VEGFR2, and PDGFRβ | Inhibits MET and RON signaling and cell growth in various cancer cell lines | Attenuates MET- and RON-mediated tumor growth in mouse tumor xenograft models | Single agent and combination with erlotinib or lapatinib for various types of advanced cancers in Phase II/III clinical trials | Phase I/II/III | Eder *et al*[82] |
| MGCD265 | MethylGene | MET, RON, VEGFR1, VEGFR2, VEGFR3, and TIE2 | Inhibits MET and RON signaling and cell growth in cancer cell lines | Attenuates MET- and RON-mediated tumor growth in mouse tumor xenograft models | Single agent and combination with erlotinib or docetaxel for NSCLC in Phase II trials | Phase I/II | Belalcazar *et al*[83] |
| BMS-777607 | Bristol-Myers Squibb | RON and MET | Inhibits MET and RON signaling, cell growth, and invasion in cancer cell lines | Inhibits MET- and RON-mediated tumor growth in mouse tumor xenograft models | Multiple ascending doses for metastatic cancers in Phase I trials | Phase I | Sharma *et al*[84] |
| MK-2461 | Merck | MET, RON, FLT1, FLT3, FGFR1, FGFR2, and FGFR3 | Inhibits MET and RON signaling, cell growth, and migration in cancer cell lines | Inhibits MET- and RON-mediated tumor growth in mouse tumor xenograft models | Antitumor efficacy is under evaluation in Phase II trials | Phase I/II | Pan *et al*[85] |
| MK-8033 | Merck | MET and RON | Inhibits MET and RON signaling, cell growth, and migration in cancer cell lines | Causes tumor regression in mouse tumor xenograft models | Safety, tolerability, dose, clinical activity and pharmaco-dynamics are under evaluation in Phase I trials | Phase I | Northrup *et al*[86] |
| PHA665752 | Pfizer | MET and RON | NA | NA | NA | Preclinical | Comoglio *et al*[87] |
| INC280 | Novartis | MET | NA | NA | NA | Phase I/II | Qin *et al*[88] |
| Tivantinib | ArQule | MET | NA | NA | NA | Phase II/III | Rimassa *et al*[89] |
| Antibody drug conjugates |  |  |  |  |  |  |  |
| Zt/g4-doxorubicin-immuoliposome | TTUHSC | RON | Moderately activates RON signaling and strongly induces RON endocytosis | No effect as naked antibody but completely inhibits tumors used as ADCs | NA | Preclinical | Guin *et al*[90] |
| Zt/g4-maytansinoid conjugate | TTUHSC | RON | Moderately activates RON signaling and strongly induces RON endocytosis | No effect as naked antibody but completely inhibits tumors used as ADCs | NA | Preclinical | Feng *et al*[91] |
| Zt/g4-MMAE | TTUHSC | RON | Moderately activates RON signaling and strongly induces RON endocytosis | No effect as naked antibody but completely inhibits tumors used as ADCs | NA | Preclinical | Yao *et al*[92] |
| H5B14-MMAE | TTUHSC | RON | NA | NA | NA | Preclinical | Yao *et al*[59] |
| SHR-A1403 | HengRui | MET | Highly potent: 0.02 to 1.5 nmol/L for cell proliferation | Xenografts and PDXs, MET over-expressed and amplified | NA | Phase I | Yang *et al*[93] |

TKIs: Tyrosine kinase inhibitors; VEGFR: Vascular endothelial growth factor receptor; PDGFR: Platelet-derived growth factor receptor; NSCLC: Non-small cell lung cancer; FGFR: Fibroblast growth factor receptor; ADC: Antibody-drug conjugate; MMAE: Monomethyl auristatin E; NA: Not available; PDX: Patient-derived xenografts.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**