# Metastasis-associated in colon cancer 1: A promising biomarker for the metastasis and prognosis of colorectal cancer (Review)

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**Abstract.** Colorectal cancer (CRC) is the fourth most frequent type of malignancy in the world. Metastasis accounts for >90% mortalities in patients with CRC. The metastasis-associated in colon cancer 1 (MACC1) gene has been identified as a novel biomarker for the prediction of metastasis and disease prognosis, particularly for patients with early-stage disease. Previous clinical studies demonstrated that MACC1 expression and polymorphisms in CRC tissues were indicators of metastasis, and that circulating transcripts in plasma were also significantly associated with the survival of patients. The present review describes the use of MACC1 beyond its utility in the clinic. By elucidating the upstream and downstream signal pathways of MACC1, the well-known mechanisms of MACC1-mediated cell proliferation, invasion, migration and epithelial-mesenchymal transition (EMT) are summarized, as well as the potential signaling pathways. Furthermore, the underlying mechanisms by which the overexpression of MACC1 causes cisplatin resistance are emphasized.

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## 1. Introduction

Colorectal cancer (CRC) is the fourth most frequent type of malignancy in the world (1). According to data collected by several authorities, including the National Cancer Institute and the National Center for Health Statistics, it was estimated that there would be 136,830 new cases of CRC and 50,310 moralities from CRC in 2014. In the United States, CRC represents 8.2% of all new cases of cancer and 8.6% of all cancer-associated mortalities.

Metastasis is the most lethal characteristic of CRC, accounting for 90% of the moralities of patients with colon cancer. The 5-year survival rates of patients with early-stage disease are up to 90%, but the 5-year survival rates of patients with distant metastasis drop to 10%. In addition, the metastatic dissemination of primary tumors is a pivotal cause for the failure of treatment (2,3). However, there is currently no molecular marker to predict the possibility of CRC metastasis in an early and precise manner (4,5).

Metastasis-associated in colon cancer 1 (MACC1), first identified by Stein *et al* (6) in 2009, is located on human chromosome 7 (7p21.1) at 20,146,776 to 20,223,538 (76,762 bp) on the minus strand, and harbors 7 exons and 6 introns. At present, five splice variants have been revealed in different types of tissue (7). In addition, the topathological description of the gene was identified by applying a combination of fold recognition and homology modeling algorithms. The results showed that the protein contains four domains, namely, ZU5, SRC Homology 3 Domain (SH3) and two C-terminal death domains (DD) (8). The SH3 domain and SH3 binding motif are responsible for the biological function of the protein. The lack of SH3 domain or the proline-rich motif SH3 binding motif will lead to the loss of the Met gene, which is a transcriptional target of MACC1 (6). The ZU5 domain is comprised of two β-sheets and is known to mediate protein-protein interactions (8-10). The unique double DD architecture may trigger apoptosis (8,11).

Stein *et al* (6) detected MACC1 mRNA expression levels in primary colon cancer. Based on the different MACC1 mRNA expression levels, the negative and positive predictions of metachronous distant metastases were corrected to 80 and 74%, respectively. The evidence suggested that MACC1 may serve

as a novel biomarker for metastasis prediction and disease prognosis, particularly for early-stage patients. Subsequently, MACC1 was also identified as the biomarker in other types of solid cancer, including gastric (12-18), lung (19-24) and breast (25-27) cancer, hepatocellular carcinoma (HCC) (28-38), ovarian cancer (39-41), renal carcinoma (42,43), glioma (44,45), gallbladder cancer (46,47), tongue squamous cell carcinoma (48), osteosarcoma (49,50), esophageal cancer (51,52), nasopharyngeal carcinoma (NPC) (53), pancreatic cancer (54), hilar cholangiocarcinoma (55), salivary adenoid cystic carcinoma (56) and cervical cancer (57) (Table I).

The present review summarizes the current studies of MACC1 in CRC (Table II) and highlights the importance of MACC1 in the prediction of therapy response and the decision of therapeutic strategy (58-70). In addition, the present review highlights the previously found mechanisms of MACC1-mediated cell proliferation, invasion, migration and epithelial-mesenchymal transition (EMT) (Table III), and the regulation of MACC1 in CRC (Fig. 1).

## 2. MACC1 is a novel biomarker for metastasis prediction and disease prognosis

*MACC1 expression in CRC.* Through the examination of MACC1 mRNA expression levels in colon mucosa, normal liver, adenoma, primary tumors and distant metastasis, a previous study illustrated that more MACC1 mRNA was expressed in malignant tissue compared with normal tissue and adenoma (P<0.0001). Comparatively, tumors with metachronous metastasis expressed significantly higher levels of MACC1 mRNA compared with those that did not metastasize (P<0.0001). More pivotally, the 5-year survival rates of patients with high and low MACC1 mRNA expression were 15 and 80%, respectively, indicating that MACC1 expression was an independent prognostic marker for colon cancer metastasis (6). Subsequently, the relevance of MACC1 expression to disease prognosis was also corroborated (58). In a clinical study with 52 CRC tumor samples available, it was revealed that MACC1 expression was significantly correlated with peritoneal dissemination (P=0.042) and the stage of tumor node metastasis classification (P=0.007). Recently, Koelzer *et al* further verified MACC1 expression as a predictive biomarker in a retrospective cohort study (67).

In addition, by examining MACC1 copy numbers and mRNA expression levels of 103 metastatic CRC tissues, it was confirmed that MACC1 expression was significantly correlated with colon cancer metastasis (71). Furthermore, the results of another study suggested that MACC1 expression was more than a prognostic marker for colon cancer metastasis, as it was also revealed to be associated with the recurrence of CRC (72), as confirmed by Nitsche *et al* (73) in 2012. According to individualized risk assessment of fresh frozen colon cancer tissue from 232 complete tumor resection patients with Union for International Cancer Control stage II disease, it was verified that the risk of cancer recurrence was markedly associated with an increased expression of MACC1 (P<0.001), independent of other biomarkers such as the mutation of KRAS proto-oncogene (73). Notably, MACC1 was the only independent parameter for recurrence prediction (hazard ratio, 6.2; P<0.001) in CRC liver metastases (62).

In addition, MACC1 was revealed to be an independent biomarker for post-operative liver metastasis in patients with colon cancer (70).

To overcome the inherent limitation of obtaining tumor tissue via an invasive method, Stein *et al* (61) described a non-invasive assay for the quantification of MACC1 transcripts in the plasma of 312 patients with CRC. The results of the aforementioned study demonstrated that MACC1 transcript levels in plasma increased in patients with all stages of cancer in comparison with tumor-free volunteers. Similar to findings in the tumor tissues, high MACC1 levels in the plasma were also correlated with unfavorable survival (P<0.0001). Qualitative studies have demonstrated that the alterations in DNA and RNA extracted from the plasma of patients are similar to the alterations of primary tumor nucleic acids, meaning that tumor cells may be the origin of plasma or serum nucleic acids (74,75). In addition, numerous studies verified the clinical value of extracellular RNA in plasma from patients with cancer (76-82), and the extracellular RNA in plasma was also revealed to be protected in a multiparticle complex and was actively released by tumor cells (83). Thus, it was hypothesized that MACC1 transcripts in plasma were released from tumor cells in a protected manner, and circulating MACC1 transcripts in plasma may be a prognostic indicator for the survival and metastasis of patients with CRC. The association between MACC1 status in the blood and patient prognosis requires additional investigation in a larger clinical study.

*MACC1 polymorphisms in CRC.* Lang *et al* (59) firstly investigated the potential association between single nucleotide polymorphisms (SNPs) of MACC1 and the survival of patients with colon cancer. A total of 318 patients with CRC were enrolled. A total of 6 tag SNPs (rs1990172, rs3114446, rs10275612, rs3095007, rs3095009 and rs7780032), representing the majority of the common variants of the MACC1 locus, were genotyped. However, only the carriers of SNP rs1990172 were revealed to exhibit an association with a significantly decreased overall survival (additive hazard ratio, 1.38; 95% CI, 1.05-1.82; P=0.023). The results of the aforementioned study indicated that SNP rs1990172 was a potential predictor for reduced overall survival in patients with CRC. Additionally, Schmid *et al* (60) sequenced the coding exons of MACC1 in 154 colorectal tumors (stages I, II and III) and found three MACC1 SNPs (rs4721888, L31V; rs975263, S515L; rs3735615, R804T) in the coding region. In addition, it was revealed that patients who were SNP rs975263 carriers, <60 years old, with stage I or II disease, exhibited an increased risk of shorter metastasis-free survival. However, none of the three SNPs were associated with clinicopathological parameters or the survival of the patients. In additional studies, the two SNPs (rs1990172 and rs975263) were associated with the clinical outcome of patients with HER2-positive breast cancer, and the recurrence and overall survival of patients with HCC undergoing liver transplantation (26,84).

However, the focus of the majority of the aforementioned studies was CRC tissue. It is difficult to reflect disease progression and response to therapy using a single type of tissue sample or a single time point (85). Circulating tumor DNA (ctDNA) was revealed to be positively correlated with tumor progression (86). In addition, ctDNA was suggested to be

Table I. Correlation of metastasis-associated in colon cancer 1 to clinical parameters in solid cancer types except colorectal cancer (in studies published from 2013 onwards).

| Tumor entity | Sample type | n | Method | Correlation to clinical parameters | (Refs.) |
|---|---|---|---|---|---|
| GC | Tumors | 436 | IHC | Invasion, metastasis, TNM stage and 5-year survival | (15) |
| | Tumors | 98 | IHC | Metastasis and overall survival | (16) |
| | Tumors | 58 | IHC | Metastasis, TNM stage and tumor formation | (97) |
| | Tumors | 190 | IHC | Lymphangiogenesis, lymphatic invasion, recurrence and overall survival | (17) |
| | Plasma | 76 | RT-qPCR | Overall survival | (18) |
| | Tumors | 88 | IHC | Overall survival | (110) |
| | Tumors | 7 | IHC | EMT | (91) |
| NSCLC | Tumors | 180 | IHC | Differentiation, TNM stage, lymph node metastasis, disease-free survival and overall survival | (23) |
| | Plasma | 272 | RT-qPCR | NSCLC stage, lymph node metastasis, disease-free survival and overall survival | (24) |
| Breast cancer | Tumors | 164 | SNP | Chemotherapy, event-free survival and overall survival | (26) |
| | Tumors | 300 | RT-qPCR and IHC | Relapse-free survival, breast cancer-specific survival and mortality | (129) |
| | Tumors | 198 | IHC | Relapse-free survival, disease-free survival and overall survival | (27) |
| HCC | Tumors | 187 | SNP | Recurrence and overall survival | (84) |
| | Tumors | 160 | RT-qPCR | Recurrence and overall survival | (34) |
| | Tumors | 60 | IHC | Edmondson classification, TNM stage and overall survival | (35) |
| | Tumors | 50 | IHC | Edmondson classification, TNM stage and overall survival | (38) |
| | Tumors | 80 | IHC | Tumor formation, Edmondson classification, TNM stage and overall survival | (36) |
| Ovarian cancer | Tumors | 52 | RT-qPCR and WB | Clinical stage and overall survival | (40) |
| | Tumors Serum | 92 | IHC ELISA | Lymph node metastasis FIGO stage and lymph node metastasis | (41) |
| Renal cancer | Tumors | 73 | IHC | TNM stage, overall survival and disease-free survival | (42) |
| | Tumors | 112 | IHC | TNM stage, metastasis and disease-free survival | (43) |
| Glioma | Tumors | 107 | RT-qPCR and IHC | Pathological grade and overall survival | (44) |
| | Tumors | 52 | RT-qPCR and IHC | WHO grade, overall survival | (45) |
| GBC | Tumors | 40 | IHC | Lymph node metastasis, perineural invasion and overall survival | (46) |
| | Tumors | 70 | IHC | Lymph node metastasis, TNM stage, perineural invasion and overall survival | (47) |
| TSCC | Tumors | 60 | IHC | Lymphatic metastasis, overall survival and cisplatin resistance | (48) |
| OS | Tumors | 116 | IHC | Clinical stage, distant metastasis and overall survival | (49) |
| Esophageal cancer | Tumors | 60 | IHC and WB | TNM stage and pathology grade | (52) |
| Pancreatic cancer | Serum | 60 | ELISA | Lymph node metastasis, distant metastasis and TNM stage | (54) |
| Klatskin tumors | Tumors | 76 | IHC | Tumor recurrence, overall survival and disease-free survival | (55) |
| SACC | Tumors | 65 | IHC | Tumor histological grading and invasion | (56) |
| Cervical cancer | Tumors | 104 | IHC | Overall survival, FIGO stage and lymph nodes metastasis | (57) |

GC, gastric cancer; HCC, hepatocellular carcinoma; GBC, gallbladder cancer; TSCC, tongue squamous cell carcinoma; SACC, salivary adenoid cystic carcinoma; TNM, tumor-node-metastasis; EMT, epithelial-mesenchymal transition; IHC, immunohistochemistry; ELISA, enzyme-linked immunosorbent assay; SNP, single nucleotide polymorphism; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; FIGO, International Federation of Gynecology and Obstetrics; WHO, World Health Organization; WB, western blotting.

an applicable, sensitive and specific biomarker in CRC (87). Therefore, the present review suggests that studies focusing on

whether MACC1 SNPs in plasma are associated with overall survival of patients with CRC patients are required. Additional

Table II. Correlation of metastasis-associated in colon cancer 1 to clinical parameters in colorectal cancer (in studies published from 2013 onwards).

| Sample type | n | Method | Correlation to clinical parameters | Country involved | (Refs.) |
|---|---|---|---|---|---|
| Tumors | 93 | IHC | Cancer initiation, invasion and distant metastasis | Rochester, USA | (63) |
| Tumors | 51 | IHC | Conventional colitis-associated colorectal cancer tumorigenesis | New York, USA | (64) |
| Tumors | 174 | RT-qPCR | Tumor invasion, distant metastasis, disease-free survival and overall survival | Osaka, Japan | (65) |
| Tumors | 99 | RT-qPCR | Metastasis-free survival | Berlin, Germany | (66) |
| Tumors | 187 | IHC | TNM stage, invasion, prediction of metastasis and allover survival | Bern, Switzerland | (67) |
| Tumors | 323 | IHC | Histological differentiation, UICC stage, TNM stage and overall survival | Guangzhou, China | (68) |
| Tumors | 96 | IHC | Lymph node metastasis, T stage and metastasis-free survival | Jinan, China | (70) |

TNM, tumor-node-metastasis; UICC, Union for International Cancer Control; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; IHC, immunohistochemistry.

studies with large sample sizes are required to reveal the potential association between MACC1 SNPs and stage classification, recurrence or prognosis.

## 3. Potential mechanisms of cell proliferation, invasion and migration induced by MACC1 in CRC cell cultures

*Upstream regulation of MACC1.* MicroRNAs (miRNAs/miRs) have been revealed to serve an important role in promoting or suppressing tumor invasion and metastasis via regulating metastasis-associated genes (88,89). Using *in silico* prediction and western blot assays, a negative correlation was identified between miR-143 and MACC1 in CRC. Through 3' untranslated region luciferase reporter gene analysis, it was revealed that miR-143 directly targeted MACC1 (90). In addition, miR-338-3p and miR-200a were also revealed to transcriptionally regulate MACC1 in gastric cancer and hepatocellular carcinoma, respectively (91,92). According to several studies (93-96), miR-338-3p and miR-200a are associated with invasion, migration, EMT and prognosis in patients with CRC. We hypothesize that they may negatively regulate MACC1 in CRC.

Stein *et al* (6) revealed that the inhibition of mitogen-activated protein kinase kinase reduced the level of MACC1 mRNA expression in the SW620 cell line, indicating that MACC1 may be regulated by the 5' adenosine monophosphate-activated protein kinase (AMPK) signal pathway. This was also revealed in a gastric cancer cell in the study by Lin *et al* (97), whereby MACC1 overexpression via the AMPK signal pathway was revealed to promote the Warburg effect by upregulating the activities and expression of a series of glycolytic enzymes in gastric cancer. These results suggest that MACC1 is a metabolic stress-responsive gene that appears to serve an important role in tumor cell resistance against stress and escaping from stress by initiating metastasis. The majority of tumors, including colon tumors, are subjected to hypoxic conditions due to the abnormal vasculature that supplies them with oxygen and nutrients. However, the deficiency of oxygen causes hypoxia-inducible factor (HIF)-1α stabilization.

Several studies confirmed that HIF-1α stabilization induced metastasis via the hepatocyte growth factor (HGF)/Met signal pathway in solid types of cancer, including CRC (98-103). In addition, nutrient or environmental stress indicated by AMPK, a highly conserved sensor of cellular energy status found in all eukaryotic cells during hypoxia (104). Based on the aforementioned information, it is possible that MACC1 may be a stress responsive gene during hypoxic stress, which may be regulated by HIF-1α stabilization in CRC. To overcome hypoxia and other metabolic stress, miR-511a and miR-483 were suppressed in metastatic colorectal cells and inhibited early metastatic colonization (105). Thus, the present study proposes that there may be an association between the two miRNAs and MACC1.

Recently, it was revealed that the cell-free DNA of tumors acts as a prometastatic factor through the induction of MACC1 via the Toll-like receptor 9 (TLR9) signaling pathway (106). TRL families serve a fundamental role in the activation of innate immunity. In particular, TLR9 signaling affects colorectal carcinogenesis and colonic inflammation (107). Notably, MACC1 is significantly associated with conventional colitis-associated colorectal cancer (CAC) tumorigenesis (64). Thus, it is hypothesized that the activation of the TRL9 signaling pathway by the cell-free DNA of tumors may respond to the stepwise upregulation of MACC1 expression from inflammatory bowel disease-associated colitis to dysplasia to adenocarcinoma.

The MACC1 promoter region from -426 to -18 was identified to be the essential domain, containing the functional binding sites for the transcription factors activator protein 1 (AP-1), specificity protein 1 (Sp1) and CCAAT-enhancer-binding protein (C/EBP). Using an electrophoretic mobility shift assay (EMSA) and a chromatin immunoprecipitation (ChIP) assay, it was additionally demonstrated that these transcription factors bound to the minimal essential MACC1 core promoter regions and regulated the transcription of the gene. In CRC tumors, the expression levels of c-Jun and Sp1 were significantly correlated with MACC1 expression levels (P=0.0007 and P=0.02, respectively) and the development of metachronous metastases

Table III. Potential mechanisms of MACC1-mediated cell proliferation, migration, invasion and EMT.

| Tumor entity | Associated gene/miR | Correlation | Potential mechanism | Correlation to clinical parameters | (Refs.) |
|---|---|---|---|---|---|
| CRC | Met | Positive | HGF/Met signaling | Metastasis-free survival, histological differentiation, UICC stage, T classification and N classification | (6,68,71,90) |
|  | β-catenin | Positive | β-catenin signaling | Histological differentiation, UICC stage, T classification and N classification | (68) |
|  | miR-143 | Negative | miR-143/MACC1 signaling | Growth, invasion and migration | (90) |
|  | Sp1/c-Jun | Positive | Binding directly | Distant metastasis | (108) |
| GC | HK2, LDH | Positive | Warburg effects and AMPK signaling | Cell growth | (97) |
|  | VEGF-C/VEGF-D | Positive | HGF/Met signaling | Cell proliferation, migration and lymphangiogenesis | (17) |
|  | TWIST1/2 | Positive | HGF/Met-TWIST1/2 signaling | Vasculogenic mimicry | (110) |
|  | miR-338-3p | Negative | miR-338-3p/MACC1/met/Akt signaling | Invasion, migration and EMT | (91) |
| NSCLC | Met | Positive | HGF/Met signaling | 5-year survival, TNM stage, recurrence and metastasis | (13-16) |
|  | Met | Positive | HGF/Met signaling | TNM stage, lymph node metastasis, disease-free survival and overall survival | (23) |
| HCC | Met | Positive | HGF/Met signaling | Disease-free survival, overall survival, median tumor-free survival and cell growth | (28,29,38) |
|  | miR-200a | Negative | Binding directly | Cell growth and metastasis | (92) |
|  | HK2 | Positive | Glucose metabolism | Cell proliferation | (36) |
| Glioma | Met | Positive | HGF/Met signaling | Proliferation, cell invasion, tumor formulation and WHO stage | (45) |
| OS | Akt | Positive | Akt signaling | Cell proliferation, colony formulation and invasion | (50) |
| NPC | Akt/β-catenin | Positive | Akt/β-catenin signaling | Clinical stage and N classification | (53) |

MACC1, metastasis-associated in colon cancer 1; NPC, nasopharyngeal carcinoma; EMT, epithelial-mesenchymal transition; UICC, Union for International Cancer Control; HGF, hepatocyte growth factor; Sp1, specificity protein 1; Akt, protein kinase B; AMPK, 5' adenosine monophosphate-activated protein kinase; TWIST, Twist family BHLH transcription factor; WHO, World Health Organization; CRC, colorectal cancer; GC, gastric cancer; miR, microRNA; HK2, hexokinase II; LDH, lactate dehydrogenase; OS, osteosarcoma; TNM, tumor-node-metastasis; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; VEGF, vascular endothelial growth factor.
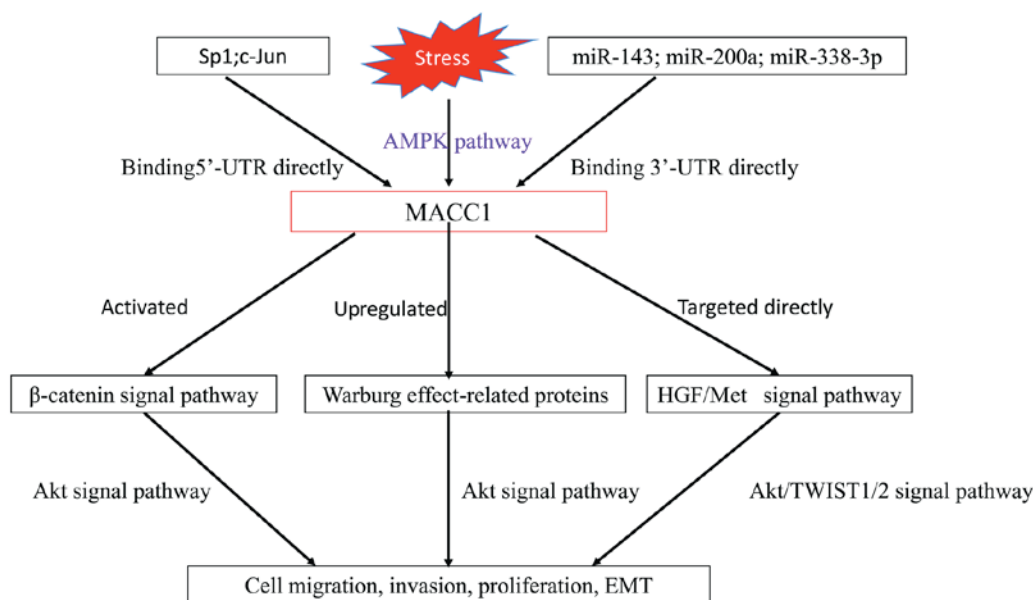
Figure 1. Potential mechanisms by which MACC1 induces cell proliferation, invasion, migration and EMT in CRC cell cultures. MACC1, metastasis-associated in colon cancer 1; EMT, epithelial-mesenchymal transition; Sp1, specificity protein 1; miR, microRNA; 3'-UTR, 3' untranslated region; AMPK, 5' adenosine monophosphate-activated protein kinase; HGF, hepatocyte growth factor; Akt, protein kinase B; TWIST, Twist family BHLH transcription factor.

(P=0.01 and P=0.001, respectively). At present, the upstream regulation of MACC1 in CRC remains unclear and requires additional investigation.

*Downstream regulation of MACC1.* Stein *et al* (6) identified a strong correlation between the levels of MACC1 and Met mRNA in stage I, II and III tumors (P=0.022). To investigate the association between MACC1 and the expression of Met, the authors analyzed the Met mRNA and protein levels in the human colon carcinoma SW480 and SW620 cell lines, which have low and high expression levels of MACC1, respectively. Though the transfection of a MACC1 overexpression vector, it was revealed that the mRNA and protein levels of Met were upregulated in the SW480 cell line. Conversely, Met was strongly downregulated subsequent to transfecting MACC1-specific small interfering RNA into the SW620 cell line. Finally, an additional study demonstrated that MACC1 combined with the promoter of the Met gene, as determined using ChIP and EMSA (109). These data suggested that the Met gene was a transcriptional target of MACC1. Subsequently, the correlation between MACC1 and Met expression was verified in CRC (6,68,69,71,90) and other cancer tissues (15-17,22,38, 39,41,45,53,91,95,110). It was revealed that MACC1 promoted tumor growth and metastasis through the HGF/Met signal pathway. However, by examining 52 matched pairs of CRC and tumorous surrounding tissues, it was found that MACC1 overexpression *per se* was not sufficient to cause the significant upregulation of Met. Notably, it was suggested that Met was significantly upregulated only when the overexpression of MACC1 was coupled with miR-1 downregulation (111).

Furthermore, Galimi *et al* (71) revealed that MACC1 expression may contribute to CRC progression through additional mechanisms such as β-catenin signaling. MACC1 expression and β-catenin abnormal expression (P=0.033) were also identified in NPC. A previous study demonstrated that MACC1 served an important role in the carcinogenesis of NPC through the protein kinase B/β-catenin signaling pathway (53). In support of this, Zhen *et al* (68) additionally revealed that MACC1 overexpression increased the expression of β-catenin, the downstream genes of MACC1, including c-Myc, cyclin D1, and MMP9, and the upstream gene of MACC1, phospho-glycogen synthase kinase 3β.

MACC1 was revealed to be was significantly associated with cisplatin resistance. The downregulation of MACC1 reduced the level of cisplatin resistance and induced apoptosis in tongue squamous cell carcinoma and human glioblastoma U251 cells (48,112). Stein *et al* (109) revealed that MACC1 functioned via binding to a special consensus sequence of Met promoter, described as a Sp1 binding site. The ATP-binding cassette sub-family G member 2 (ABCG2) promoter region exhibited the same consensus sequence and the inhibition of Sp1-dependent ABCG2 expression caused chemosensitization to cisplatin (113). Therefore, it is possible that ABCG2 may be a transcriptional target of MACC1, and cisplatin resistance may be caused by the increase of ABCG2 induced by the overexpression of MACC1. Recently, multiple studies showed that the activation of the Wnt/β-catenin pathway enhanced cisplatin resistance, whereas Wnt/β-catenin pathway inhibition sensitized cancer cells to cisplatin (114-118). Overall, the Wnt/β-catenin pathway serves a critical role in cisplatin resistance and MACC1 overexpression may enhance cisplatin resistance via activing the Wnt/β-catenin pathway.

MACC1 has been demonstrated to promote vasculogenic mimicry (VM) by upregulating Twist family BHLH transcription factor (TWIST)1/2 through the HGF/Met signal pathway in gastric cancer (110). TWIST1/2 were revealed to be associated with EMT and were also valuable biomarkers in CRC (119,120). Thus, it was hypothesized that MACC1 induced EMT via the HGF/MET/TWIST1/2 signal pathway in CRC.

Despite advances with regard to our understanding of the association between MACC1 expression and the survival

of patients with CRC, little is known about the mechanisms behind the induction of cell proliferation, invasion and migration by MACC1 in CRC cell cultures. It is therefore necessary to identify these complex internal mechanisms.

## 4. Conclusions

In CRC, metastasis is the most frequent cause of treatment failure and it is responsible for 90% of patient mortality. However, there is no molecular biomarker sufficient for predicting the risk of tumor progression and metastasis. Numerous studies have revealed that MACC1 expression and SNPs are correlated with metastasis-free survival. Therefore, MACC1 status may be regarded as a tumor stage-independent predictor for CRC metastasis.

Met, identified as a transcriptional target of MACC1, is associated with CRC metastasis (121-129). However, MACC1 induces colon cancer cell growth, invasion and migration not only by the HGF/Met signal pathway, but also by the β-catenin signal pathway. Additionally, miRNA (miR-143) and several transcription factors (AP-1, Sp1, and C/EBP) have been revealed to be involved in the negative or positive regulation of MACC1. However, the specific mechanism behind the upstream regulation of MACC1 remains unclear.

Based on the clinical and experimental evidence of MACC1 in CRC, it may be considered as a promising biomarker for the prediction of CRC metastasis and disease prognosis. Several studies have reported that the downregulation of MACC1 inhibits colorectal tumor progression and metastasis in CRC cells and xenografted mice (6,90,130). MACC1 may also act as a therapeutic target in the treatment of CRC. Due to the significantly higher expression of MACC1 in CRC tissues compared with other organs, enteric-coated products targeting MACC1 may be a good treatment strategy. However, little was previously known with regard to how MACC1 functions in CRC. The specific mechanisms of MACC1 should be additionally investigated, and MACC1-based retrospective studies or interventional strategies should be developed in larger clinical trials of CRC.

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