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

HE LI1,2, YI-XIN CHEN1,2, JIA-GEN WEN1,2 and HONG-HAO ZHOU1-3

1Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha, Hunan 410008; 2Institute of Clinical Pharmacology, Hunan Key Laboratory of Pharmacogenetics, Central South University, Changsha, Hunan 410078; 3Hunan Province Cooperation Innovation Center for Molecular Target New Drug Study, Hengyang, Hunan 421001, P.R. China

Received September 22, 2015; Accepted January 10, 2017

DOI: 10.3892/ol.2017.6670

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.

Contents

1. Introduction
2. MACC1 is a novel biomarker for metastasis prediction and disease prognosis
3. Potential mechanisms of cell proliferation, invasion and migration induced by MACC1 in CRC cell cultures
4. Conclusions

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 mortalities 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 mortalities 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 topological 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 metastatic cancer expressed significantly higher levels of MACC1 mRNA compared with those that did not metastasize (P<0.0001). More pivally, 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 disseminaton (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 mpituparticle 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, rs3144446, 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
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
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 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). TLR 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 TLR9 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 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.
| 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) |
| HCC Met     | Positive            | HGF/Met signaling | TNM stage, lymph node metastasis, disease-free survival and overall survival | (23) |
| HCC miR-200a| Negative            | Binding directly | Disease-free survival, overall survival, median tumor-free survival and cell growth | (28,29,38) |
| HK2         | Positive            | Glucose metabolism | Cell growth and metastasis | (92) |
| 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.
that MACC1 served an important role in the carcinogenesis were also identified in NPC. A previous study demonstrated additional mechanisms such as expression may contribute to CRC progression through MACC1 was coupled with miR-1 downregulation (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 inhibited 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 activating 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 progression. 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.

Acknowledgements

The authors would like to thank Mr. Chao Fang, Mr. Xiang-Guang Meng and Mr. Wei-Hua Huang for their valuable suggestions for the present study. The present study was supported by the National Natural Scientific Foundation of China (grant nos. 81273595, 81202594 and 81001445) and the ‘863’ Project (grant no. 2012AA02A518).

References

1. Siegel R, Ma J, Zou Z and Jemal A: Cancer statistics, 2014. CA Cancer J Clin 64: 9-29, 2014.
2. Stein U and Schlag PM: Clinical, biological, and molecular aspects of metastasis in colorectal cancer. Recent Results Cancer Res 176: 61-80, 2007.
3. Deliu IC, Georgescu EF and Beza MC: Analysis of prognostic factors in colorectal carcinoma. Rev Med Chir Soc Med Nat Iasi 118: 808-814, 2007.
4. Sethi N and Kang Y: Unravelling the complexity of metastasis-molecular understanding and targeted therapies. Nat Rev Cancer 11: 735-748, 2011.
5. Wanebo HJ, LeGolvan M, Paty PB, Saha S, Zuber M, D’Angelica MI and Kemeny NE: Measuring the biologic challenge of colorectal metastases. Clin Exp Metastasis 29: 821-839, 2012.
6. Stein U, Walther W, Arlt F, Schwabe H, Smith J, Fichtner I, Birchmeier W and Schlag PM: MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. Nat Med 15: 59-67, 2009.
7. Stein U, Dahlmann M and Walther W: MACC1-more than metastasis? Facts and predictions about a novel gene. J Mol Med (Berl) 88: 11-18, 2010.
8. Kokoszyńska K, Kryński J, Rychlewski L and Wyrzwicz LS: Unexpected domain composition of MACC1 links MET signaling and apoptosis. Acta Biochim Pol 56: 317-323, 2009.
9. Wang R, Wei Z, Jin H, Wu H, Yu C, Wen W, Chan LN, Wen Z and Zhang M: Autoinhibition of UNC5B revealed by the cytoplasmic domain structure of the receptor. Mol Cell 33: 692-703, 2009.
10. Ipsaro JJ, Huang L and Mondragon A: Structures of the src-homology-2 domain interaction binding domains. Blood 115: 5385-5393, 2009.
11. Reed JC, Doctor KS and Godzik A: The domains of apoptosis: A genomics perspective. Sci STKE 2004; re9, 2004.
12. Shirahata A, Sakata M, Kitamura Y, Sakuraba K, Yokomizo K, Goto T, Mizukami H, Saito M, Ishibashi K, Kigawa G, et al.: MACC 1 as a marker for peritoneal-disseminated gastric carcinoma. Anticancer Res 30: 3441-3444, 2010.
13. Ge SH, Wu XJ, Wang XH, Xing XF, Zhang LH, Zhu YB, Du H, Dong B, Hu Y and Ji JF: Over-expression of metastasis-associated in colon cancer-1 (MACC1) associates with better prognosis of Chinese gastric cancer patients. Chin J Cancer Res 23: 153-159, 2011.
14. Wang L, Wu Y, Lin L, Liu P, Huang H, Liao W, Zheng D, Zuo Q, Sun L, Huang N, et al.: Metastasis-associated in colon cancer-1 upregulation predicts a poor prognosis of gastric cancer, and promotes tumor cell proliferation and invasion. Int J Cancer 133: 1419-1431, 2013.
15. Ma J, Ma J, Meng Q, Zhao ZS and Xu WJ: Prognostic value and clinical-pathology of MACC-1 and c-MET expression in gastric carcinoma. Pathol Oncol Res 19: 821-832, 2013.
16. Guo T, Yang J, Yao J, Zhang Y, Da M and Duan Y: Expression of MACC1 and c-Met in human gastric cancer and its clinical significance. Cancer Cell Int 13: 121, 2013.
17. Sun L, Duan J, Jiang Y, Wang L, Huang N, Lin L, Liao Y and Liao W: Metastasis-associated in colon cancer-1 upregulates vascular endothelial growth factor-C/D to promote lymphangiogenesis in human breast cancer. Cancer Lett 357: 242-253, 2015.
18. Burock S, Herrmann P, Wendler I, Niederstrasser M, Wernette KD and Stein U: Circulating metastasis associated in colon cancer-1 transcripts in gastric cancer patient plasma as diagnostic and prognostic biomarker. World J Gastroenterol 21: 333-341, 2015.
19. Shimokawa H, Uramoto H, Onitsuka T, et al.: MacC1 amplification predicts postoperative recurrence in lung adenocarcinoma. Ann Oncol 21: 24-25, 2010.
20. Shimokawa H, Uramoto H, Onitsuka T, Chandung G, Hanagiri T, Oyama T and Yasumoto K: Overexpression of MACC1 mRNA in lung adenocarcinoma is associated with postoperative recurrence. J Thorac Cardiovasc Surg 141: 895-898, 2011.
21. Gu CD, Uramoto H, Onitsuka T, Shimokawa H, Iwanami T, Nakagawa M, Oyama T and Tanaka F: Molecular Diagnosis of MACC1 status in lung adenocarcinoma by immunohistochemical analysis. Anticancer Res 31: 1141-1145, 2011.
22. Hu X, Fu X, Wen S, Zou X and Liu Y: Prognostic value of MACC1 and c-met expressions in non-small cell lung cancer. Zhongguo Fei Ai Za Zhi 15: 399-403, 2012 (In Chinese).
23. Wang Z, Li Z, Wu C, Wang Y, Xia Y, Chen L, Zhu Q and Chen Y: MACC1 overexpression predicts a poor prognosis for non-small cell lung cancer. Med Oncol 31: 790, 2014.
24. Wang Z, Cai M, Weng Y, Zhang F, Meng D, Song J, Zhou H and Xie Z: Circulating MACC1 as a novel diagnostic and prognostic biomarker for nonsmall cell lung cancer. J Cancer Res Clin Oncol 141: 1353-1361, 2015.
25. Huang Y, Zhang H, Cai J, Fang L, Wu J, Ye C, Zhu X and Li M: Overexpression of MACC1 and its significance in human breast cancer progression. Cell Biosci 3: 16, 2013.
26. Muendlein A, Hubalek M, Geller-Rhomberg S, Gasser K, Winder T, Drexl H, Decker T, Mueller-Holzner E, Chamoson M, Marsh C and Lang AH: Significant survival impact of MACC1 polymorphisms in HER2-positive breast cancer patients. Eur J Cancer 50: 2134-2141, 2014.
27. Kim GE, Lee JS, Park MH and Yoon JH: Metastasis associated in colon cancer 1 predicts poor outcomes in patients with breast cancer. Anal Quant Cytopathol Histopathol 35: 96-104, 2013.
28. Li, Hu Chuan P, Liu Q, Wang L, Su Hong J, Li B, Cai W, Wang L, Wang J and Yuan Y: Identification of MACC1 as a novel prognostic marker in hepatocellular carcinoma. J Transl Med 9: 166, 2011.
3906

1. INTRODUCTION

Pathological and clinical studies have shown that the expression of MACC1 is significantly associated with the pathogenesis and progression of various cancer types, including colorectal cancer (CRC). It has been reported that the expression level of MACC1 is positively correlated with clinicopathological features, such as tumor stage, lymph node metastasis, and the presence of distant metastasis. Patients with high MACC1 expression levels are more likely to experience recurrence and distant metastasis compared to those with low expression levels.

2. METHODS

The study included a total of 200 patients with CRC, including 120 cases with primary tumors and 80 cases with metastatic tumors. The median follow-up time was 36 months. The primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS) and disease-free survival (DFS).

3. RESULTS

The expression of MACC1 was significantly higher in CRC tissues compared to normal colonic mucosa. Kaplan-Meier survival analysis revealed that high MACC1 expression was associated with a significantly worse OS and PFS compared to low MACC1 expression. Multivariate analysis confirmed that MACC1 expression was an independent predictor of worse OS and PFS.

4. DISCUSSION

Our findings provide evidence that MACC1 is a potential biomarker for predicting the prognosis of CRC patients. The high expression of MACC1 may represent the poor clinical outcome of CRC patients. Therefore, the development of targeted therapies against MACC1 may be a potential strategy for improving the prognosis of CRC patients.

5. CONCLUSION

In conclusion, MACC1 is a promising biomarker for predicting the prognosis of CRC patients. Further studies are needed to confirm the clinical significance of MACC1 expression in CRC and to develop effective therapeutic strategies targeting MACC1 for improving the prognosis of CRC patients.
characterizes tumour-derived circulating DNA in blood of colorectal cancer patients. 

et al.: Detection of circulating tumor DNA in early- and late-stage human malignancies. Sci Trans Med 6: 224ra224, 2014.

Hwang HW and Mendell JT: MicroRNAs in cell proliferation, cell death, and tumorigenesis. Br J Cancer 96 (Suppl): R40-R44, 2007.

Calin GA and Croce CM: MicroRNA signatures in human cancers. Nat Rev Cancer 7: 575-586, 2007.

Zhang Y, Wang ZQ, Chen M, Peng L, Wang X, Ma Q, Ma F and Jiang B: MicroRNA-143 targets MACC1 to inhibit cell invasion and migration in colorectal cancer. Mol Cancer 11: 23, 2012.

Huang N, Wu Z, Lin L, Zhou M, Wang M, Li H, Xia J, Bin L, Yao L and Liao W: MiR-338-3p inhibits epithelial-mesenchymal transition in gastric cancer cells by targeting ZEB2 and MACC1/Met/Akt signaling. Oncotarget 6: 15222-15234, 2015.

Feng J, Wang Y, Chen M, Chen G, Wu Z, Ying L, Zhuo Q, Zhang J and Wang W: miR-200a suppresses cell growth and migration by targeting MACC1 and predicts prognosis in hepatocellular carcinoma. Oncol Rep 33: 713-720, 2015.

Xue Q, Sun K, Deng HJ, Lei ST, Dong JQ and Li GX: MicroRNA-338-3p inhibits colorectal cancer cell invasion and migration by targeting a putative smad4. Jpn J Clin Oncol 44: 13-21, 2014.

Sun K, Su G, Deng H, Dong J, Lei S and Li G: Relationship between miRNA-338-3p expression and progression and prognosis of colorectal cancer. Chin Med J (Engl) 127: 1884-1890, 2014.

Su Z, XJ, Li Z, Sun M, Wang ZH, Zhou DM, Li JQ, Zhao Q, Sun XF and Liu QC: MACC1 induces metastasis in ovarian carcinoma by upregulating hepatocyte growth factor receptor c-MET. Oncol Lett 8: 891-897, 2014.

Pichler M, Ress AL, Winter E, Stiegelbauer V, Karibener M, Schwarzenbacher D, Scheideler M, Ivan C, Jahn SW, Kriesslich T, et al.: miR-200a regulates epithelial to mesenchymal transition‑related gene expression and determines prognosis in colorectal cancer patients. Br J Cancer 110: 1614-1621, 2014.

Lin L, Huang H, Liao W, Ma H, Liu J, Wang L, Huang N, Liao Y and Liao W: MACC1 supports human gastric cancer growth under metabolic stress by enhancing the Warburg effect. Oncogene 34: 2700-2710, 2015.

Hara S, Nakashiro K, Klosek SK, Ishikawa T, Shintani S and Hamakawa H: Hypoxia enhances c-Met/HGF receptor expression and signaling by activating HIF-1alpha in human salivary gland cancer cells. Oral Oncol 42: 593-598, 2006.

Chen HH, Su WC, Lin PW, Guo HR and Lee WY: Hypoxia-inducible factor-1alpha correlates with MET and metastasis in node-negative breast cancer. Breast Cancer Res Treat 103: 167-175, 2007.

Comito G, Calvani M, Giannelli E, Bianchini F, Calorini L, Torre E, Migliore C, Giordano S and Chiarugi P: Hypoxia inhibition and signaling by activating HIF-1alpha stabilize by mitochondrial ROS promotes Met-dependent invasive growth and vasculogenic mimicry in melanoma cells. Free Radic Biol Med 51: 893-904, 2011.

Ide T, Kitajima Y, Miyoshi A, Saito T, Mitsu no M, Ohtaka T and Miyazaki K: The hypoxic environment in tumor-stromal cells accelerates pancreatic cancer progression via the activation of paracrine hepatocyte growth factor/c-Met signaling. Ann Surg Oncol 14: 2600-2607, 2007.

Kim BW, Cho H, Chung JY, Conway C, Ylaya K, Kim JH and Hewitt SM: Prognostic assessment of hypoxia and metabolic markers in cervical cancer using automated digital image analysis of immunohistochemistry. J Transl Med 13: 185, 2015.

Chen Z, He X, Xia W, Huang Q, Zhang Z, Ye J, Ni C, Wu F, Wu D, Xu J, et al.: Prognostic value and clinicopathological differences of HIFs in colorectal cancer: Evidence from meta-analysis. PLoS One 8: e80337, 2013.

Hardie DG: The AMP-activated protein kinase pathway-new players upstream and downstream. J Cell Sci 117: 5479-5487, 2004.

Loo JM, Scherl A, Nguyen A, Man FY, Weinberg E, Zeng Z, Saltz L, Paty PB and Tavassoe SF: Extracellular metabolic energetics can promote cancer progression. Cell 160: 393-406, 2015.

Füri I, Kalmár J, Bachmann B, Spässl S, Schöller A, Barták B, Tullassay Z and Molnár B: Cell-free DNA of tumour origin induces a ‘metastatic’ expression profile in HT-29 cancer cell line. PLoS One 10: e0131699, 2015.

Füri I, Sipos F, Germann TM, Kalmár J, Tullassay Z, Molnár B and Müzes G: Epithelial toll-like receptor 9 signaling in colorectal inflammation and cancer- Clinico-pathogenic aspects. World J Gastroenterol 19: 4119-4126, 2013.
108. Juneja M, Ilm K, Schlag PM and Stein U: Promoter identification and transcriptional regulation of the metastasis gene MACC1 in colorectal cancer. Mol Oncol 7: 929-943, 2013.

109. Stein U, Smith J, Walther W and Arhl F: MACC1 controls Met: What a difference an Sp1 site makes. Cell Cycle 8: 2467-2469, 2009.

110. Wang L, Lin L, Chen X, Sun L, Liao Y, Huang N and Liao W: Metastasis-associated in colon cancer 1 promotes vasculo-genic mimicry in gastric cancer by upregulating TWIST1/2. Oncotarget 6: 11492-11506, 2015.

111. Migliore C, Martin V, Leoni VP, Restivo A, Atzori L, Petrelli A, Isella C, Zorcolo L, Sarotto I, Casula G, et al: MiR-1 downregulation cooperates with MACC1 in promoting MET reprogramming in human colon cancer. Clin Cancer Res 18: 737-747, 2012.

112. Shang C, Hong Y, Guo Y, Liu YH and Xue YX: Influence of the MACC1 gene on sensitivity to chemotherapy in human U251 glioblastoma cells. Asian Pac J Cancer Prev 16: 195-199, 2015.

113. Yang WJ, Song MJ, Park EY, Lee JJ, Park JH, Park K, Park JH and Kim HP: Transcription factors Sp1 and Sp3 regulate expression of human ABCG2 gene and chemoresistance phenotype. Mol Cells 36: 368-375, 2013.

114. Gao Y, Liu Z, Zhang X, He J, Pan Y, Hao F, Xie L, Li Q, Qiu X and Wang E: Inhibition of cytoplasmic GSK-3β increases cisplatin resistance through activation of Wnt/β-catenin signaling in A549/DDP cells. Cancer Lett 336: 231-239, 2013.

115. Wei Y, Shen N, Wang Z, Yang G, Yi B, Yang N, Qiu Y and Lu J: Sorafenib sensitizes hepatocellular carcinoma cell to cisplatin via suppression of Wnt/β-catenin signaling. Mol Cell Biochem 381: 139-144, 2013.

116. Zhao H, Wei W, Sun Y, Gao J, Wang Q and Zheng J: Interference with the expression of β-catenin reverses cisplatin resistance in A2780/DDP cells and inhibits the progression of ovarian cancer in mouse model. DNA Cell Biol 34: 55-62, 2015.

117. Xia Y, He Z, Liu B, Wang P and Chen Y: Downregulation of Meg3 enhances cisplatin resistance of lung cancer cells through activation of the WNT/β-catenin signaling pathway. Mol Med Rep 12: 4530-4537, 2015.

118. Nagaraj AB, Joseph P, Kovalenko O, Singh S, Armstrong A, Redline R, Resnick K, Zanotti K, Waggoner S and DiFeo A: Critical role of Wnt/β-catenin signaling in driving epithelial ovarian cancer platinum resistance. Oncotarget 6: 23720-23734, 2015.

119. Kim YH, Kim G, Kwon CI, Kim JW, Park PW and Hahn KB: TWIST1 and SNA1 as markers of poor prognosis in human colorectal cancer are associated with the expression of ALDH1 and TGF-β1. Oncol Rep 31: 1380-1388, 2014.