

The metastasis-associated in colon cancer-1 (MACC1) gene was identified in 2009. Expression of MACC1 was found to be significantly upregulated in primary and metastatic colon carcinomas compared to normal tissues or adenomas. The induction of MACC1 occurs at the crucial step of transition from a benign to a malignant phenotype.

The aim of this review was to summarise current results of non-clinical and clinical studies on the role of MACC1 in the carcinogenesis and progression of cancer, as well its potential therapeutic and prognostic significance.

The gene encoding the HGF receptor MET is a transcriptional target of MACC1. In addition to promoting the proliferation, invasion, and migration of colon cancer cells in cell culture and tumour growth and metastasis in mouse models, MACC1 also contributes to carcinogenesis and progression of colorectal cancer through the β -catenin signalling pathway and mesenchymal-epithelial transition.

MACC1 knockdown with si/sh RNA was investigated in cell lines of different types of cancer. MACC1 is a promising therapeutic target for antitumour and antimetastatic intervention strategies for cancers. Here, it is presented as a potential independent prognostic indicator of reduced overall survival as well as of the occurrence of distant metastasis in patients with different types of cancer.

Key words: metastasis-associated in colon cancer-1 (MACC1), cancer therapy, prognosis.

Contemp Oncol (Pozn) 2016; 20 (4): 273–280
DOI: 10.5114/wo.2016.61846

The potential therapeutic applications and prognostic significance of metastasis-associated in colon cancer-1 (MACC1) in cancers

Ewa Katarzyna Kopczyńska

Department of Pathobiochemistry and Clinical Chemistry, Faculty of Pharmacy, Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz, Poland

Introduction

The metastasis-associated in colon cancer-1 (MACC1) was identified by a genome-wide search for differentially expressed genes in primary and metastatic colon carcinomas [1].

Expression of MACC1 was found to be significantly upregulated in malignant tissues (colon cancer at all stages as well as liver and lung metastases) compared to normal tissues (colon mucosa, liver) or adenomas. The induction of MACC1 occurs at the crucial step of transition from a benign to a malignant phenotype [2].

The aim of this review was to summarise current results of non-clinical and clinical studies on the role of MACC1 in the carcinogenesis and progression of cancer, as well its potential prognostic and therapeutic usefulness.

MEDLINE via the PubMed database was searched in order to locate and select data, using pre-defined terms for English-language articles, published up to and including July 15, 2015. The terms used as descriptors were “MACC1”, “cancer”, “progression”, “prognosis”, and “therapy”.

The role of the metastasis-associated in colon cancer-1 in cancer initiation, invasiveness, and metastasis

The significance of MACC1 in tumourigenesis and development of an aggressive phenotype has been investigated mainly in colorectal cancer.

The role of MACC1 in colorectal cancer progression

MACC1 is a major regulator of its transcriptional target gene, MET [1]. After binding hepatocyte growth factor (HGF), Met activates the HGF/Met signalling pathway, resulting in growth, epithelial-mesenchymal transition (EMT), angiogenesis, invasiveness, and metastasis [3]. MACC1 promotes the proliferation, invasion, and migration of colon cancer cells in cell culture and tumour growth and metastasis in mouse models [1].

The specific Sp1 binding site of the human MET promoter was identified as essential for MACC1-induced activation of the Met tyrosine kinase receptor and subsequent HGF/Met signalling consequences. In the event of activation by HGF, c-MET transmits intracellular signals and activates downstream Ras-mitogen-activated protein kinase (MAPK)/Erk and phosphoinositide 3-kinase (PI3K)/AKT pathways, consequently promoting cell survival, migration, and invasion, and suppressing apoptosis [4]. *In silico* and *in vitro* studies [5] revealed that the MACC1 promoter contains potential binding sites for various transcription factors, including Sp1, AP-1, and C/EBP,

which participate in the transcription of genes involved in tumourigenesis, cell growth, and metastasis. Oncogenic transcription factors Sp1 and AP-1 have been found to be overexpressed in most cancers, including colorectal cancer.

The application of a combination of fold recognition and homology modelling algorithms revealed that the MACC1 protein consists of four domains: ZU5, Src-homology 3 (SH3), and two C-terminal death domains (DD). Structural modelling of MACC1 has revealed an unexpected domain composition (ZU5-DD) with direct links to regulation of apoptosis [6]. Another study [7] proved the role of two domains: the SH3-domain and proline-rich motif (PXXP) in protein-specific interactions. To estimate the impact of the SH3-domain in MACC1 for tumourigenesis and metastasis formation, Pichorner *et al.* [8] analysed SW480-derived transfectants lacking the SH3-domain (SW480/luc-MACC1 DSH3) capacity for cell motility in cell culture and monitored development of tumours and metastases in mice. Tumour growth and metastasis were reduced.

MACC1 may also contribute to carcinogenesis and progression of colorectal cancer through the β -catenin signalling pathway and mesenchymal-epithelial transition. MACC1 overexpression increases β -catenin mRNA and protein expression in HCT116 cells compared with an empty-vector control group. It also induces β -catenin downstream genes including *c-Myc* (a promoter of cell cycle and apoptosis), *cyclin D1* (a regulator of cell cycle progression), and metalloproteinase (MMP) 9 (invasion factor) and suppresses cleaved caspase-3 expression (promoter of apoptosis). MACC1 knockdown inhibits cellular proliferation, migration, invasion, colony formation, and tumourigenesis, both *in vitro* and *in vivo*, but induces apoptosis in colorectal cancer cells [9].

MACC1 expression has been associated with the transition from adenoma to carcinoma and the invasive growth of early colorectal cancer. Stepwise elevation of MACC1 expression suggests that it may contribute to cancer initiation (transition from adenoma to carcinoma) and early invasive growth [10].

Koelzer *et al.* [11] performed a 'geographic' analysis of MACC1 expression in colorectal cancer with a particular focus on EMT-like cancer cells in the tumour microenvironment, also called tumour buds. MACC1 was variably expressed in normal mucosa, tumour centre, invasive front, and tumour buds. MACC1 was significantly over-expressed in tumour tissue as compared to normal mucosa. In tumour tissue, a gradient of MACC1 expression from the tumour centre to the invasive front was identified. In tumour buds, a strong cytoplasmic expression was observed. No MACC1 expression was observed in the tumour stroma. In the tumour centre, MACC1 expression (score 1–3) was observed in 58% of cases. MACC1 positivity in the tumour centre further predicted aggressive tumour growth with the presence of lymphatic invasion, venous invasion, and frequent metastasis to loco regional lymph nodes. Furthermore, MACC1 expression in the tumour centre was highly correlated with the presence of high-grade tumour budding. However, no impact of MACC1 expression in the tumour centre on the frequency of distant metastasis or patient survival was observed. At the tumour front, MACC1

expression was observed in 72% of cases. MACC1 staining at the tumour front was seen in aggressive tumours with more advanced pT-stage, presence of lymphatic and venous invasion, as well as frequent nodal metastasis. MACC1 expression at the tumour front was strongly predictive for the formation of distant metastasis. Strong MACC1 expression at the invasive front correlated with a high-grade tumour budding phenotype. MACC1 expression was observed in 55% of tumour buds and correlated with aggressive disease biology [11].

The association of MACC1 expression with the KRAS G12 and KRAS G13 was confirmed [12]. The most frequent point mutations in codon 12 (KRAS G12) and 13 (KRAS G13) of exon 2 result in constitutive activation of KRAS and downstream pathways. The high MACC1 expression and KRAS G13 mutation are independent prognostic markers for metachronous metastases development [12].

The role of MACC1 in gastric cancer progression

MACC1 causes important molecular changes in gastric cancer (GC) cell lines. In cDNA microarray experiments, 33 up-regulated and 24 downregulated genes were identified in cells following MACC1 transfection, which was involved in various cellular functions [13]. MACC1 promoted the proliferation, migration, and invasion of gastric cancer cell lines. Overexpression of MACC1 induced tumour growth and metastasis in athymic mice. Additionally, gastric MACC1 mRNA expression level was correlated with markers of epithelial-mesenchymal transition (E-cadherin, fibronectin, and vimentin) in patients with gastric cancer [14].

MACC1 promotes gastric cancer cell proliferation and invasion by inducing the epithelial-mesenchymal transition (EMT) through activation of the HGF/*c-Met* signalling pathway. In addition, HGF induces nuclear translocation of MACC1, which is required for its biological activity, while the EMT is known to play a pivotal role in tumourigenesis and in vasculogenic mimicry (VM) [15]. Wang *et al.* [15] hypothesised that MACC1 has a role in the process of VM in gastric cancer. MACC1 expression was positively correlated with VM density and with the expression of vascular endothelial cadherin (VE-cadherin), an important regulator of VM. MACC1 promoted both VM and tumour progression. MACC1 upregulated TWIST1/2 (TWIST1 is a key regulator of the EMT, and is biologically and clinically linked to VM in tumours; TWIST2 has a similar sequence to TWIST1, but its role in the process of VM is unknown). Silencing of TWIST1 and TWIST2 significantly reduced tube formation by GC cells, indicating that these molecules play a central role in MACC1-induced vasculogenic mimicry. MACC1 promotes VM in GC by regulating the HGF/*c-Met*-TWIST1/2 signalling pathway, which means that MACC1 and this pathway are potential new therapeutic targets for gastric cancer.

MACC1 upregulated vascular endothelial growth factor-C/-D to promote lymphangiogenesis *in vivo* and *in vitro*. Additionally, the HGF/*Met* signalling pathway was involved in MACC1-mediated lymphangiogenesis [16]. MACC1 expression was significantly upregulated by adenosine monophosphate-activated protein kinase signal-

Table 1. The molecular intervention impact on cancer cell proliferation and metastatic capacity

Cancer cell line	Molecular intervention strategy	Changes of signalling pathway contributors after si/shRNA transfection	Impact on cancer function	Ref.
Hepato-cellular Huh7 cells	shRNA	Downregulation of Met, MMP2, MMP9 proteins expression	Reduction of cell migration and invasion abilities	[18]
Gallbladder cancer cells	siRNA	–	Reduction of cell proliferation, anchorage-independent growth, and cell migration	[22]
Pancreatic cancer CEPAC-1 cells	siRNA	Downregulation of Ras and ERK1/2 expression	Inhibition of cell proliferation, migration, and epithelial-mesenchymal transition Downregulation of MACC1 sensitised CFPAC-1 cells to gemcitabine	[23]
Naso-pharyngeal cancer CNE2 cells	siRNA	Inhibition of phosphorylated-Akt (Ser473) and β -catenin expression	Inhibition of cellular proliferation, migration, invasion, and colony formation Induction of apoptosis	[24]
Ovarian cancer OVCAR3 cells	siRNA	Reduction of Met protein expression	Downregulation of invasive, metastatic and angiogenic capacities of the cells	[25]
Ovarian cancer OVCAR3 cells	shRNA	Reduction of Met, MEK1/2, ERK1/2, cyclin D1 and MMP2 protein expression. Induction of cleaved caspase-3 level	Inhibition of cell proliferation, migration and invasion Induction of apoptosis	[26]
Cervical cancer SiHa cells	siRNA	Reduction of cyclin D1, Cdk2, MMP2, MMP9 proteins expression. Upregulation of p21 and E-cadherin protein expression	Suppression of cell proliferation, alteration of cell cycle distribution, reduction of cell invasion ability	[27]
Cervical cancer HeLa cells	siRNA	–	Reduction of cell proliferation or migration Induction of apoptosis	[28]
Osteo-sarcoma U2OS cells	siRNA	Inactivation of Akt signalling pathway	Inhibition of cell proliferation <i>in vitro</i> , colony formation, invasion and tumour growth <i>in vivo</i> Induction of apoptosis	[29]
Glioma U251 cells	shRNA	Cell cycle arrest at G1 phase The main regulatory targets: cyclins D1 and E Inhibition of enzymatic activities of MMP-2 and MMP-9	Inhibition of cell proliferation, invasion, and migration Enhancement of apoptosis	[30]

ling in response to metabolic stress induced by glucose deprivation. MACC1 promoted the Warburg effect by up-regulating the activity and expression of a series of glycolytic enzymes in gastric cancer cells. This metabolic shift enhanced cell viability and resistance to apoptosis by facilitating ATP generation, reducing reactive oxygen species production, and stabilising mitochondrial membrane potential [17].

The role of MACC1 in hepatocellular carcinoma progression

MACC1 was highly expressed in hepatocellular carcinoma (HCC) tissues, and the nuclear expression of MACC1 protein was associated with poor tumour differentiation and intrahepatic metastasis or portal invasion. MACC1 protein was localised in both nuclei and cytoplasm of HCC cell lines, and the nuclear localisation of MACC1 protein was associated with increased aggressiveness of HCC in cell lines (Hep3B, Huh7, MHCC97H, SMMC-7721, Bel-7402, and HepG2) [18].

MACC1 inhibits cell apoptosis in hepatocellular carcinoma by the activation of the HGF/c-MET/PI3K/AKT pathway and phosphorylation of anti-apoptotic proteins including BAD, caspase 9, and FKHL1 [19].

The potential role of MACC1 inhibition in cancer therapy

Molecular intervention strategies applied in cancer therapy include small molecule inhibitors, antibodies, and RNA-based technologies such as small interfering RNA (siRNA) or small hairpin RNA (shRNA). These compounds target key molecules of tumourigenesis and metastasis, such as cancer-related kinases.

The HGF/Met signaling pathway contributes to metastasis formation. Currently, this pathway is targeted with specific monoclonal antibodies and small molecules to neutralize HGF or block the Met receptor [20]. For instance, treatment of cervix cancer with Taxol causes inhibition of tumour growth and reduces expression levels of MACC1, HGF and Met proteins, and MACC1 mRNA in the tumour tissue of cervical carcinoma mice [21].

Targeting MACC1, a key regulator of HGF/Met signaling, may have a particular therapeutic impact in colorectal cancer. The first *in vivo* studies of Stein *et al.* [1] with si/sh RNAs demonstrated significant reductions in tumour size and number of liver metastases. Similarly, Pichorner *et al.* [8] observed a reduction in tumour growth and metastasis formation in SW620 cell-xenografted mice by using MACC1 shRNA.

MACC1 knockdown with si/sh RNA was also investigated in cell lines of other types of cancer (Table 1) [18, 22–30].

Hurst *et al.* [31] proposed a novel group of cancer-related miRNAs, termed metastamiRs, associated with metastatic processes. MetastamiRs represent potential candidate prognostic biomarkers and therapeutic targets for metastatic cancers. The findings of Zhang *et al.* [32] suggest that miR-143 may function as a metastamiR by targeting MACC1. Researchers have proven a regulatory relationship between miR-143, a known tumour-suppressive miRNA, and the new oncogene MACC1. Using online miRNA target prediction databases (*miRNA.org* and *Targetscan*), they hypothesised that MACC1 was a target of miR-143. Downregulation of miR-143 by inhibitors in SW480 cells led to a moderate increase in MACC1 protein level. Thus, miR-143 was able to impede colorectal cancer cell invasion and migration, at least partly by targeting MACC1. The treatment of SW620 cells with MACC1 siRNA, in combination with miR-143 mimics, produced synergistic inhibitory effects on MACC1 expression, cellular growth, migration, and invasion ability when compared to either MACC1 siRNA or miR-143-mimic treatment alone. Additionally, researchers proved that miR-143 levels were inversely correlated with MACC1 mRNA expression in colorectal cancer tissues.

Tumour-suppressive MiR-1 and miR-200a, similarly to miR-143, could contribute to the development of cancer controlled by MACC1 [33, 34]. Concurrent MACC1 upregulation and miR-1 downregulation are required to elicit the highest increase in Met expression. MiR-1 contributes to colorectal cancer by controlling Met expression [33]. MiR-200a suppressed tumour growth and metastasis by directly targeting MACC1 in hepatocellular cancer [34].

MiR-338-3p was originally identified as contributing to the basolateral polarity formation in epithelial cells. It may participate in the epithelial-mesenchymal transition regulation, which requires cytoskeleton remodelling and motor activity. MiR-338-3p suppresses EMT by targeting the MACC1/Met/Akt pathway in gastric cancer cells. MACC1 is directly inhibited by the binding of miR-338-3p to its 3'UTR, leading to the suppression of EMT [35].

RNA interference (RNAi) against MACC1 and suppressive microRNAs may constitute a promising intervention strategy for gene therapy for cancer.

The diagnostic and prognostic significance of MACC1 in different types of cancer

MACC1 expression has been found in colorectal carcinoma (ca), gastric ca, hepatocellular ca, gallbladder ca, pancreatic ca, oesophageal ca, nasopharyngeal ca, lung ca, breast ca, ovarian ca, cervical ca, renal ca, glioma, and osteosarcoma. Overexpression of MACC1 correlates with the progression of these cancers and negative prognosis for the patients.

Usefulness of MACC1 in colorectal cancer

The dependence between MACC1 expression and clinicopathological features in colorectal cancer patients is not clear. MACC1 expression has been significantly related to histological differentiation, UICC stage, and T and N

classifications [9]. In another study [36] the absence of significant correlations between MACC1 mRNA expression and patient gender, age, histology, maximal tumour size, extent of tumour, lymph node metastasis, or liver metastasis was observed. Nevertheless, MACC1 expression correlated with peritoneal dissemination and an elevated stage of TNM classification. MACC1 was more frequently expressed in advanced cancers. MACC1 is being presented as a potential independent prognostic indicator for reduced overall survival as well as for the occurrence of distant metastasis in colorectal cancer patients [1, 37–40]. MACC1 mRNA expression has been identified [1] in predicting the development of metachronous distant metastases in not-yet-metastasised primary colon cancers (negative 80%, positive 74%). MACC1 expression was significantly higher in primary tumours that subsequently developed distant metastases compared to those that did not metastasise within a 10-year follow-up period. MACC1 levels were prognostic for metastasis-free survival of patients. The five-year survival of patients with low MACC1 expression in their primary tumour was 80%, compared to 15% when high levels were detected. Thus, MACC1 represents an early prognostic indicator for colon cancer metastasis. Another study [38] revealed the prognostic impact of MACC1 mRNA expression in metastatic colorectal cancer following curative liver resection: high MACC1 levels were associated with significantly higher rates of recurrence within 36 months. MACC1 overexpression was the only factor among biomarkers (KRAS, BRAF, MMR, osteopontin, SASH1) in a panel associated (to a highly significant degree) with distant metastases, thus serving as an independent predictor for formation of metachronous metastasis [39]. Overexpression of MACC1 correlated more closely than overexpression of Met with unfavourable pathologic features. The prognostic power of MACC1 in predicting metastasis-free survival was higher than that of Met; moreover, a combination of MACC1 and Met expression failed to improve the accuracy of the prognosis either for metastasis or for five-year survival. MACC1 is a stronger prognostic factor than Met. It has been suggested that transcripts other than Met can be regulated by MACC1 and may contribute to an aggressive phenotype associated with high MACC1 levels [40].

The diagnostic and prognostic value of circulating MACC1 transcripts in patient plasma for metastasis and survival was also investigated [41]. Identification of the highest levels of circulating MACC1 transcripts in individuals with metastases demonstrates their diagnostic value, while high MACC1 levels correlate with unfavourable patient survival rates. Thus, MACC1 represents a promising target for anti-metastatic therapies, and circulating MACC1 transcripts could be used to monitor therapeutic response in cancer patients.

Three MACC1 single-nucleotide polymorphisms (SNPs) in the coding region were genotyped [42]. The identification of coding MACC1 SNPs in primary colorectal tumours does not improve predictions for metastasis formation or for patients' survival compared to MACC1 expression analysis alone. By contrast, Lang *et al.* [43] proved that, among investigated SNPs, variant rs1990172 was significantly

associated with an increased risk of death. This finding suggests the clinical relevance of MACC1 as a prognostic marker gene, which may help to select high-risk patients for more aggressive treatment strategies.

Usefulness of MACC1 in gastric cancer

Research data concerning the correlation between MACC1 expression and clinicopathological features in gastric cancer patients are equivocal. In some studies [16, 17, 44–46], positive expression of MACC1 was correlated with patient age [44], tumour size [44], depth of invasion [44], lymph node and distant metastases [16, 17, 44, 45], TNM stage [44], peritoneal dissemination [46], and more advanced disease [16]. In other studies [46, 47], or by contrast [44, 45], no significant correlations were observed between MACC1 expression and patient gender [44–46], age [45, 46], differentiation or histological classification [44, 46, 47], tumour size [46], extent of tumour [45–47], lymphatic invasion [46], venous invasion [46, 47], lymph node metastasis [45, 46], distant metastasis [16, 45, 46], hepatic metastasis [45], peritoneal metastasis [45], TNM stage [16, 45–47], or Lauren's classification [44].

Correlation analysis of MACC1 protein expression and gastric cancer patient prognosis revealed that the five-year survival rate of patients with stage I–III expressing high levels of MACC1 was significantly poorer than those expressing low levels of these proteins [44]. Higher levels of expression were associated with more frequent postoperative recurrence and a higher mortality rate. Disease-free survival rates for patients with stage I–III and overall survival rates of patients with stage IV were significantly worse when their tumours showed high MACC1 expression [16]. By contrast, in a study by Ge *et al.* [47], the survival difference between positive and negative MACC1 expression groups was not statistically significant.

In the latest studies (2015), Burock *et al.* [48] reported the diagnostic and prognostic value of circulating MACC1 transcripts in the blood of patients with gastric cancer. Levels of MACC1 were significantly higher at each disease stage when compared with tumour-free volunteers and were prognostic for gastric cancer patient survival. Patients with high MACC1 transcript levels had poorer overall survival rates compared with patients with low levels. The combination of two biomarkers, MACC1 and S100A4 (biomarker of metastasis), improved the accuracy of prognoses compared to analyses based on each individual biomarker.

Usefulness of MACC1 in hepatocellular cancer

The levels of MACC1 mRNA [18] and protein product [18, 49] were higher in hepatocellular cancer (HCC) cells than in normal liver cells.

MACC1 expression in HCC was compared with clinicopathological features [18, 49–51]. Positive expression of MACC1 [49–51] and high intratumoural MACC1 mRNA levels [18, 49] were associated with a high Edmondson-Steiner classification [50], advanced TNM stage [18, 49], progression of HCC [18], and tumour differentiation [18]. High MACC1 expression was significantly correlated with higher

serum AFP, which is a biomarker of HCC invasiveness and an unfavourable prognosis [50–52]. These dependences suggest that MACC1 expression may be an indicator of more aggressive behaviour on the part of HCC.

Data from studies [18, 49, 50, 52–54] indicate that MACC1 may be an independent prognostic factor of HCC.

Recent [55] meta-analysis showed that MACC1 over-expression was significantly associated with poor overall survival and poor disease-free survival in HCC patients. MACC1 over-expression was significantly associated with AFP level, tumour number, differentiation, TNM stage, vascular invasion, capsule invasion, and metastasis. The authors of this meta-analysis concluded that MACC1 over-expression indicates poor survival rate, high recurrence rate, and aggressive biological behaviours. MACC1 can serve as an indicator of prognosis and a potential novel target for treatment in HCC patients.

Genetic variations of the MACC1 gene were examined as predictors of recurrence and overall survival of HCC patients treated with liver transplantation [56]. Polymorphisms of rs1990172 and rs975263 were significantly associated with tumour recurrence in HCC patients undergoing transplantation.

Usefulness of MACC1 in digestive system neoplasms

Wu *et al.* [57] demonstrated the prognostic value of MACC1 in digestive system neoplasms (colorectal cancer, gastric cancer, oesophageal cancer, pancreatic cancer, and hepatocellular carcinoma). The evidence provided by this systematic review and meta-analysis suggests that MACC1 might serve as a prognostic biomarker for digestive system neoplasms. High MACC1 expression significantly correlated with poorer overall survival as well as poorer relapse-free survival.

The prognostic significance of MACC1 has been investigated not only in colorectal, gastric, and hepatocellular cancers, but also in others (Table 2) [1, 9, 16, 18, 22–24, 36, 44–47, 49, 50, 52, 53, 58–64, 66–70].

Usefulness of MACC1 in breast cancer

Correlations of MACC1 expression with primary tumours, lymph node metastasis, distant metastasis classifications, and clinical staging in breast cancer patients were found [64]. No correlations were found between MACC1 expression and patient age, ER and PR status, or HER2 status [64].

Overexpression of MACC1 was associated with both reduced recurrence-free survival and reduced overall survival. Stratification of breast cancer patients according to oestrogen receptor (ER) status revealed that MACC1 was prognostic for both ER-negative and ER-positive patients [64].

Three MACC1 single-nucleotide polymorphisms, rs1990172, rs975263, and rs3735615, in HER2-positive breast cancer were genotyped [65]. MACC1 variant rs1990172 was associated with menopausal status. All three SNPs were associated with chemotherapy. Genotypes with rare alleles of SNP rs1990172 (GC, GG) and SNP rs975263 (CT, TT), respectively, showed a significantly increased risk of progression or death.

Table 2. The dependence between MACC1 expression and clinicopathological features in cancer patients

Cancer	The correlation of MACC1 protein/mRNA expression with demographic and clinicopathological features						
	Patient age	Gender	Histopathology	TNM or other staging	Prognostic significance		Ref.
					Lower OS	Lower DFS	
Colorectal carcinoma	no	no	no	no	–	–	[36]
	–	–	yes	yes	–	–	[9]
	–	–	–	–	yes	yes	[1, 37–40]
Gastric carcinoma	yes	no	no	yes	yes	–	[44]
	no	no	no	no	–	–	[45–47]
	–	–	–	–	yes	yes	[16]
Hepatocellular carcinoma	–	–	yes	yes	–	–	[18, 49]
	–	–	–	–	yes	yes	[49, 50, 52, 53]
Gallbladder carcinoma	no	no	yes	yes	yes	–	[22]
Pancreatic carcinoma	no	no	–	yes	–	–	[23]
Oesophageal carcinoma	no	no	no	yes	yes	–	[58, 59]
Naso-pharyngeal carcinoma	no	no	no	yes (only N)	–	–	[24]
Lung carcinoma	no	no	yes	yes	–	–	[60, 63]
	–	–	–	–	yes	yes	[60–62]
Breast carcinoma	–	–	–	yes	yes	yes	[64]
Ovarian carcinoma	–	–	–	yes	yes	–	[66]
Cervical carcinoma	–	–	–	yes	yes	–	[67]
Renal carcinoma	–	–	yes	yes	yes	yes	[68]
Glioma	no	no	yes	no	yes	–	[69]
Osteosarcoma	no	no	–	yes	yes	–	[71]

SNP rs1990172, SNP rs975263, and SNP rs3735615 remained significantly associated with disease-free survival and overall survival.

In conclusion, increasing amounts of evidence suggest that overexpression of MACC1 is associated with development and progression in many tumours. MACC1 is a promising therapeutic target for antitumour and antimetastatic intervention strategies for cancers. Overexpression of MACC1 protein and mRNA may represent a potentially useful biomarker for the prognoses of cancer patients.

The authors declare no conflict of interest.

References

- Stein U, Walther W, Arlt F, et al. MACC1, a newly identified key regulator of HGF-MET signaling, predicts colon cancer metastasis. *Nat Med* 2009; 15: 59-67.
- Arlt F, Stein U. Colon cancer metastasis: MACC1 and Met as metastatic pacemakers. *Int J Biochem Cell Biol* 2009; 41: 2356-9.
- Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. *Nat Rev Mol Cell Biol* 2003; 4: 915-25.
- Stein U, Smith J, Walther W, Arlt F. MACC1 controls Met – what a difference an Sp1 site makes. *Cell Cycle* 2009; 8: 2467-9.
- Juneja M, Ilm K, Schlag PM, Stein U. Promoter identification and transcriptional regulation of the metastasis gene MACC1 in colorectal cancer. *Mol Oncol* 2013; 7: 929-43.
- Kokoszyńska K, Kryński J, Rychlewski L, Wyrwicz LS. Unexpected domain composition of MACC1 links MET signaling and apoptosis. *Acta Biochim Pol* 2009; 56: 317-23.
- Stein U, Dahlmann M, Wather W. MACC1 – more than metastasis? Facts and predictions about a novel gene. *J Mol Med (Berl)* 2010; 88: 11-8.
- Pichorner A, Sack U, Kobelt D, et al. In vivo imaging of colorectal cancer growth and metastasis by targeting MACC1 with shRNA in xenografted mice. *Clin Exp Metastasis* 2012; 29: 573-83.
- Zhen T, Dai S, Li H, Yang Y, Kang L, Shi H, Zhang F, Yang D, Cai S, He Y, Liang Y, Han A. MACC1 promotes carcinogenesis of colorectal cancer via β -catenin signaling pathway. *Oncotarget* 2014; 5: 3756-69.
- Ren B, Zakharov V, Yang Q, McMahon L, Yu J, Cao W. MACC1 is related to colorectal cancer initiation and early-stage invasive growth. *Am J Clin Pathol* 2013; 140: 701-7.
- Koehler VH, Herrmann P, Zlobec I, Karamitopoulou E, Lugli A, Stein U. Heterogeneity analysis of Metastasis Associated in Colon Cancer 1 (MACC1) for survival prognosis of colorectal cancer patients: a retrospective cohort study. *BMC Cancer* 2015; 15: 160.
- Ilm K, Kemmner W, Osterland M, Burock S, Koch G, Herrmann P, Schlag PM, Stein U. High MACC1 expression in combination with mutated KRAS G13 indicates poor survival of colorectal cancer patients. *Mol Cancer* 2015; 14: 38.
- Wang N, Xie JM, Zheng DY, Zuo Q, Liao WJ. Establishment of BGC-823/pBaBb-puro-MACC1 gastric cancer cell line stably expressing MACC1 and its tumour-related gene expression profiles. (Abstract) *Nan Fang Yi Ke Da Xue Xue Bao* 2012; 32: 312-6.
- Wang L, Wu Y, Lin L, et al. Metastasis-associated in colon cancer-1 upregulation predicts a poor prognosis of gastric cancer, and promotes tumour cell proliferation and invasion. *Int J Cancer* 2013; 133: 1419-30.

15. Wang L, Lin L, Chen X, Sun L, Liao Y, Huang N, Liao W. Metastasis-associated in colon cancer-1 promotes vasculogenic mimicry in gastric cancer by upregulating TWIST1/2. *Oncotarget* 2015; 6: 11492-506.
16. Sun L, Duan J, Jiang Y, et al. Metastasis-associated in colon cancer-1 upregulates vascular endothelial growth factor-C/D to promote lymphangiogenesis in human gastric cancer. *Cancer Lett* 2015; 357: 242-53.
17. Lin L, Huang H, Liao W, et al. MACC1 supports human gastric cancer growth under metabolic stress by enhancing the Warburg effect. (Abstract) *Oncogene* 2015; 34: 2700-10.
18. Gao J, Ding F, Liu Q, Yao Y. Knockdown of MACC1 expression suppressed hepatocellular carcinoma cell migration and invasion and inhibited expression of MMP2 and MMP9. *Mol Cell Biochem* 2013; 376: 21-32.
19. Yao Y, Dou C, Lu Z, Zheng X, Liu Q. MACC1 suppresses cell apoptosis in hepatocellular carcinoma by targeting the HGF/c-MET/PI3K/AKT pathway. *Cell Physiol Biochem* 2015; 35: 983-96.
20. Eder JP, Vande Woude GF, Boerner SA, LoRusso PM. Novel therapeutic inhibitors of the c-Met signaling pathway in cancer. *Clin Cancer Res* 2009; 15: 2207-14.
21. Chen XP, Lan JY, Chen YG, Shen ZJ. Analysis of HGF, MACC1, C-met and apoptosis-related genes in cervical carcinoma mice. *Mol Biol Rep* 2014; 41: 1247-56.
22. Wang Y, Hong Q, Wang J, Fang Y, Hu C. Downregulated expression of metastasis associated in colon cancer 1 (MACC1) reduces gallbladder cancer cell proliferation and invasion. *Tumour Biol* 2014; 35: 3771-8.
23. Wang G, Kang MX, Lu WJ, Chen Y, Zhang B, Wu YL. MACC1: A potential molecule associated with pancreatic cancer metastasis and chemoresistance. *Oncol Lett* 2012; 4: 783-91.
24. Meng F, Li H, Shi H, et al. MACC1 down-regulation inhibits proliferation and tumorigenicity of nasopharyngeal carcinoma cells through Akt/ β -catenin signaling pathway. *PLoS One* 2013; 8: e60821.
25. Sheng XJ, Li Z, Sun M, et al. MACC1 induces metastasis in ovarian carcinoma by upregulating hepatocyte growth factor receptor c-MET. *Oncol Lett* 2014; 8: 891-7.
26. Zhang R, Shi H, Chen Z, Wu Q, Ren F, Huang H. Effects of metastasis-associated in colon cancer 1 inhibition by small hairpin RNA on ovarian carcinoma OVCAR-3 cells. *J Exp Clin Cancer Res* 2011; 30: 83.
27. Hua F, Xia Y, Wang H, et al. Effects of small interfering RNA silencing MACC-1 expression on cell proliferation, cell cycle and invasion ability of cervical cancer SiHa cells. *Zhonghua Zhong Liu Za Zhi* 2014; 36: 496-500.
28. Chai H, Yang Y. Effects of MACC1 siRNA on biological behaviors of HeLa. *Arch Gynecol Obstet* 2014; 289: 1271-80.
29. Zhang K, Tian F, Zhang Y, et al. MACC1 is involved in the regulation of proliferation, colony formation, invasion ability, cell cycle distribution, apoptosis and tumorigenicity by altering Akt signaling pathway in human osteosarcoma. *Tumour Biol* 2014; 35: 2537-48.
30. Sun L, Li G, Dai B, Tan W, Zhao H, Li X, Wang A. Silence of MACC1 expression by RNA interference inhibits proliferation, invasion and metastasis, and promotes apoptosis in U251 human malignant glioma cells. *Mol Med Rep* 2015; 12: 3423-31.
31. Hurst DR, Edmonds MD, Welch DR. Metastamir: the field of metastasis-regulatory microRNA is spreading. *Cancer Res* 2009; 69: 7495-8.
32. Zhang Y, Wang Z, Chen M, et al. MicroRNA-143 targets MACC1 to inhibit cell invasion and migration in colorectal cancer. *Mol Cancer* 2012; 11: 23.
33. Migliore C, Martin V, Leoni VP, et al. MiR-1 downregulation cooperates with MACC1 in promoting MET overexpression in human colon cancer. *Clin Cancer Res* 2012; 18: 737-47.
34. Feng J, Wang J, Chen M, et al. miR-200a suppresses cell growth and migration by targeting MACC1 and predicts prognosis in hepatocellular carcinoma. *Oncol Rep* 2015; 33: 713-20.
35. Huang N, Wu Z, Lin L, et al. MiR-338-3p inhibits epithelial-mesenchymal transition in gastric cancer cells by targeting ZEB2 and MACC1/Met/Akt signaling. *Oncotarget* 2015; 6: 15222-34.
36. Shirahata A, Shinmura K, Kitamura Y, et al. MACC1 as a marker for advanced colorectal carcinoma. *Anticancer Res* 2010; 30: 2689-92.
37. Yamamoto H, Miyoshi N, Mimori K, et al. MACC1 expression levels as a novel prognostic marker for colorectal cancer. *Oncol Lett* 2014; 8: 2305-9.
38. Isella C, Mellano A, Galimi F, et al. MACC1 mRNA levels predict cancer recurrence after resection of colorectal cancer liver metastases. *Ann Surg* 2013; 257: 1089-95.
39. Nitsche U, Rosenberg R, Balmert A, et al. Integrative marker analysis allows risk assessment for metastasis in stage II colon cancer. *Ann Surg* 2012; 256: 763-71.
40. Galimi F, Torti D, Sassi F, et al. Genetic and expression analysis of MET, MACC1, and HGF in metastatic colorectal cancer: response to met inhibition in patient xenografts and pathologic correlations. *Clin Cancer Res* 2011; 17: 3146-56.
41. Stein U, Burock S, Herrmann P, et al. Circulating MACC1 transcripts in colorectal cancer patient plasma predict metastasis and prognosis. *PLoS One* 2012; 7: e49249.
42. Schmid F, Burock S, Klockmeier K, Schlag PM, Stein U. SNPs in the coding region of the metastasis-inducing gene MACC1 and clinical outcome in colorectal cancer. *Mol Cancer* 2012; 11: 49.
43. Lang AH, Geller-Rhomberg S, Winder T, et al. A common variant of the MACC1 gene is significantly associated with overall survival in colorectal cancer patients. *BMC Cancer* 2012; 12: 20.
44. Ma J, Ma J, Meng Q, Zhao ZS, Xu WJ. Prognostic value and clinical pathology of MACC-1 and c-MET expression in gastric carcinoma. *Pathol Oncol Res* 2013; 19: 821-32.
45. Guo T, Yang J, Yao J, Zhang Y, Da M, Duan Y. Expression of MACC1 and c-Met in human gastric cancer and its clinical significance. *Cancer Cell Int* 2013; 13: 121.
46. Shirahata A, Sakata M, Kitamura Y, et al. MACC 1 as a marker for peritoneal-disseminated gastric carcinoma. *Anticancer Res* 2010; 30: 3441-4.
47. Ge SH, Wu XJ, Wang XH, et al. Over-expression of metastasis-associated in Colon Cancer-1 (MACC1) associates with better prognosis of gastric cancer patients. *Chin J Cancer Res* 2011; 23: 153-9.
48. Burock S, Herrmann P, Wendler I, Niederstrasser M, Wernecke KD, Stein U. Circulating metastasis associated in colon cancer 1 transcripts in gastric cancer patient plasma as diagnostic and prognostic biomarker. *World J Gastroenterol* 2015; 21: 333-41.
49. Ji D, Lu ZT, Li YQ, et al. MACC1 expression correlates with PFKFB2 and survival in hepatocellular carcinoma. *Asian Pac J Cancer Prev* 2014; 15: 999-1003.
50. Qiu J, Huang P, Liu Q, et al. Identification of MACC1 as a novel prognostic marker in hepatocellular carcinoma. *J Transl Med* 2011; 9: 166.
51. Shirahata A, Fan W, Sakuraba K, et al. MACC 1 as a marker for vascular invasive hepatocellular carcinoma. *Anticancer Res* 2011; 31: 777-80.
52. Xie C, Wu J, Yun J, et al. MACC1 as a prognostic biomarker for early-stage and AFP-normal hepatocellular carcinoma. *PLoS One* 2013; 8: e64235.
53. Yang YP, Qu JH, Chang XJ, et al. High intratumoural metastasis-associated in colon cancer-1 expression predicts poor outcomes of cryoablation therapy for advanced hepatocellular carcinoma. *J Transl Med* 2013; 11: 41.
54. Gao S, Lin BY, Yang Z, et al. Role of overexpression of MACC1 and/or FAK in predicting prognosis of hepatocellular carcinoma after liver transplantation. *Int J Med Sci* 2014; 11: 268-75.
55. Sun DW, Zhang YY, Qi Y, Liu GQ, Chen YG, Ma J, Ly GY. Prognostic and clinicopathological significance of MACC1 expression in hepatocellular carcinoma patients: a meta-analysis. *Int J Clin Exp Med* 2015; 8: 4769-77.
56. Zheng Z, Gao S, Yang Z, et al. Single nucleotide polymorphisms in the metastasis-associated in colon cancer-1 gene predict the recurrence of hepatocellular carcinoma after transplantation. *Int J Med Sci* 2014; 11: 142-50.
57. Wu Z, Zhou R, Su Y, Sun L, Liao W. Prognostic value of MACC1 in digestive system neoplasms: A systematic review and meta-analysis. *Biomed Res Int* 2015; 2015: 252043. doi: 10.1155/2015/252043.

58. Wang JJ, Hong Q, Hu CG, Fang YJ, Wang Y. Significance of MACC1 protein expression in esophageal carcinoma. (Abstract) *Zhonghua Yi Xue Za Zhi* 2013; 93: 2584-6.
59. Zhu M, Xu Y, Mao X, Gao Y, Shao L, Yan F. Overexpression of metastasis-associated in colon cancer-1 associated with poor prognosis in patients with esophageal cancer. *Pathol Oncol Res* 2013; 19: 749-53.
60. Wang Z, Li Z, Wu C, et al. MACC1 overexpression predicts a poor prognosis for non-small cell lung cancer. *Med Oncol* 2014; 31: 790.
61. Chundong G, Uramoto H, Onitsuka T, et al. Molecular diagnosis of MACC1 status in lung adenocarcinoma by immunohistochemical analysis. *Anticancer Res* 2011; 31: 1141-5.
62. Shimokawa H, Uramoto H, Onitsuka T, et al. Overexpression of MACC1 mRNA in lung adenocarcinoma is associated with post-operative recurrence. *J Thorac Cardiovasc Surg* 2011; 141: 895-8.
63. Hu X, Fu X, Wen S, Zou X, Liu Y. Prognostic value of MACC1 and c-met expressions in non-small cell lung cancer. (Abstract) *Zhongguo Fei Ai Za Zhi* 2012; 15: 399-403.
64. Huang Y, Zhang H, Cai J, et al. Overexpression of MACC1 and its significance in human breast cancer progression. *Cell Biosci* 2013; 3: 16.
65. Muendlein A, Hubalek M, Geller-Rhomberg S, et al. Significant survival impact of MACC1 polymorphisms in HER2 positive breast cancer patients. *Eur J Cancer* 2014; 50: 2134-41.
66. Zhang RT, Ren F, Shi HR. Expression of metastasis-associated in colon cancer-1 in different stages of epithelial ovarian cancer. (Abstract) *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2014; 36: 47-51.
67. Guo L, Lu W, Zhang X, Luo D, Zhang H. Metastasis-associated colon cancer-1 is a novel prognostic marker for cervical cancer. *Int J Clin Exp Pathol* 2014; 7: 4150-5.
68. Hu H, Tian D, Chen T, Han R, Sun Y, Wu C. Metastasis-associated in colon cancer 1 is a novel survival-related biomarker for human patients with renal pelvis carcinoma. *PLoS One* 2014; 9: e100161.
69. Yang T, Kong B, Kuang YQ, et al. Overexpression of MACC1 protein and its clinical implications in patients with glioma. *Tumour Biol* 2014; 35: 815-9.
70. Hagemann C, Fuchs S, Monoranu CM, et al. Impact of MACC1 on human malignant glioma progression and patients' unfavorable prognosis. *Neuro Oncol* 2013; 15: 1696-709.
71. Zhang K, Zhang Y, Zhu H, et al. High expression of MACC1 predicts poor prognosis in patients with osteosarcoma. *Tumour Biol* 2014; 35: 1343-50.

Address for correspondence

Ewa Katarzyna Kopczyńska

Department of Pathobiochemistry and Clinical Chemistry
Collegium Medicum in Bydgoszcz
M. Curie-Skłodowskiej 9
85-094 Bydgoszcz, Poland
e-mail: kopczynska@cm.umk.pl

Submitted: 11.05.2015

Accepted: 20.07.2015