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Review Article

Metastasis associated in colon cancer 1 (MACC1): at the crossroads of cancer metastasis and drug resistanced

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Abstract: Metastasis and drug resistance are the greatest contributors to cancer related death. Thus, identification of the effective targets becomes the essential prerequisite for individualized diagnosis and therapy. MACC1 is a transcription factor that promotes tumor metastasis and drug resistance. In this review, the discovery of MACC1 is briefly presented. We reviewed MACC1 accelerates metastasis in multiple types of cancer through promoting the HGF/c-Met signaling pathway, EMT process, lymphangiogenesis and vasculogenic mimicry. MACC1 induces drug resistance by enhancing metabolic shift. In addition, we envisioned that the utility of MACC1 as a potential prognostic biomarker and a promising therapeutic target for suppressing cancer metastasis and drug resistance.

Keywords: MACC1, metastasis, drug resistance, prognosis

Introduction

Cancer metastasis and drug resistance results from several selective forces, and are closely correlated with the clinical outcomes of cancer patients [1-5]. Thus, identification of the effective targets becomes the essential prerequisite for individualized diagnosis, prognosis and therapy. Metastasis associated in colon cancer-1 (MACC1) was identified recently in colon cancer through genome-wide expression analysis [6]. MACC1 promotes many types of cancer cell proliferation, migration and invasion in cell culture, metastasis in mice model [6-9]. Overexpression of MACC1 is associated with poor prognosis in a wide variety of tumor types [10-13]. Recent studies have shown that MACC1 promotes Warburg effect by enhancing the expressions and activities of a series of glycolytic enzymes, including hexokinase (HK), pyruvate dehydrogenase kinase (PDK) and lactate dehydrogenase (LDH) in gastric cancer cells [14]. Meanwhile, overexpression of MACC1 was also involved in drug resistance and enhanced Warburg effect through activation of PI3K/AKT signaling pathway [15]. In this review, the discovery of MACC1 is briefly presented. We reviewed different mechanisms by which MACC1 promotes metastasis and drug resistance in solid cancer. In addition, we envisioned that the utility of MACC1 as a potential prognostic biomarker and a promising therapeutic target for suppressing cancer metastasis and drug resistance.

The overview of MACC1

MACC1 was identified by genome-wide analysis from colon cancer tissues in 2009 [6]. MACC1 was associated with cancer proliferation, migration, invasion in cell culture and tumor metastasis in mice model. MACC1 was demonstrated as a strong prognostic marker for many types of solid tumor [16]. *MACC1* gene is located on chromosome 7p21.1, including 7 exons and 6 introns, 3188 bp mRNA encode a protein containing 852 amino acids [6]. Study showed that there are multiple single nucleotide polymorphism (SNPs) changes in MACC1 genes, most of them occurs in the conserved region [17].

MACC1 protein is characterized by variety of domains. These domains enable MACC1 involved in several signaling pathways transduction [18]. N terminal consisting of 130-150 amino acids, encode several conserved motifs which

serve in protein-protein interactions. For instance, clathrin box, two Epsin 15 homology motif (EH) interactions sites and AP2α binding site. A ZU5 domain was identified which previously has been found in receptor and cytoskeletal proteins. C terminal domain including 2 death domain (DD). This suggests that MACC1 involved in the regulation of apoptosis. The domain and related domains family can mediate the process of immunity, inflammatory reaction, migration and apoptosis; SH domain, there is Src homology domain (SH domain) between ZU5 domain and terminal C. SH3 also involved in signal transduction through binding to the K/RXXPXXP sequence where it combine with the proline consensus sequence as the ligand [6].

MACC1 and cancer metastasis

MACC1 promotes metastasis through HGF/c-Met signal pathway

Chromatin immunoprecipitation assay (ChIP) and Electrophoretic Mobility Shift Assay (EMAS) confirmed MACC1 regulate the expression of MET gene which encodes the Hepatocyte Growth Factor Receptor (HGFR, c-Met) [6]. The HGF/c-Met signal pathway plays an important role in normal embryonic development and injury repair process, however, excessive activation of HGF/c-Met pathway is closely related to cell proliferation, process of epithelial mesenchymal transformation (EMT), tumor angiogenesis, cancer cell migration, invasion and metastasis [6]. It's found that excessive activation of HGF/c-Met pathway lead to tumorigenesis and metastasis in colon cancer [19], breast cancer [20], liver cancer [21], ovary caner [22], melanoma [23] and thyroid cancer [24]. As the significant biomarker for tumor prognosis and early-prediction of metastasis, c-Met was phosphorylated after combining with HGF, and promoted cells proliferation, migration, invasion and inhibiting apoptosis through MAPK and PI3K-Akt pathway [25, 26]. Although numerous of signal pathways involved in the regulation of c-Met expression such as Notch pathway, MACC1 as transcription factors plays a crucial role in regulation of c-Met expression [6]. MACC1 bound to the promoter of MET, this proximal promoter is consisted of 60 bp containing the consensus sequence of Sp-1, AP-2 and KLF-4, which are the regulating factors of MET [6, 27]. Thereby, MACC1 could regulate the transcription of MET by these specific consensus sequences. It is demonstrated that MACC1 can dramatically enhance c-Met expression, enhance the tumor tissue sensibility to HGF, activate tumor cell malignant behavior depending on c-Met and result in tumorigenesis and hepatic metastasis in SCID mice [6, 8, 28, 29]. Knockdown the expression of MACC1 decreased the c-Met expression level, and inhibited the proliferation, migration and metastasis of tumor cells [6, 7]. Besides, the Grb2-Ras-MAPK pathway is also the downstream target of the HGF/c-Met pathway, MACC1 activates Ras-Rho-Rac G-protein family and is involved in the MAPK signal pathway through the protein-protein interaction induced by SH3 domain [6]. Thus, MACC1 promotes metastasis through HGF/c-Met signaling pathway.

MACC1 promotes EMT

Wang et al [30] first reported that MACC1 mRNA expression was correlated with markers of EMT in tumor tissues of gastric cancer patients. They found that overexpression MACC1 significantly upregulated expression of fibronectin, MMP2, MMP9, vimentin and CD44. In contrast, inhibition of MACC1 repressed the expression of fibronectin, MMP2, MMP9, vimentin and CD44, whereas upregulated E-cadherin and α-catenin. Moreover, MACC1 overexpression significantly accelerated tumor proliferation, migration and invasion and promotes metastasis of gastric cancer *in vivo*.

Zhen et al [31] confirmed that MACC1 and β-catenin expression were higher in colorectal cancer cells and tissues than those in normal colonic epithelial cell line and adjacent non-tumor tissues. Inhibition of MACC1 dramatically suppressed cellular proliferation, migration, invasion and tumorigenesis *in vitro* and *in vivo*. Further, MACC1 overexpression increased c-Met, β-catenin and vimentin expression, suggested that MACC1 serve as a key factor in carcinogenesis and progression of colorectal cancer through β-catenin signaling pathway and EMT pathway.

MACC1 facilitates vasculogenic mimicry

Blood supply is a critical factor for tumor metastasis [32], vasculogenic mimicry (VM) is the dominant approach that provides the blood supply in the early stage of cancer and is also

an important route of metastasis [33]. Thus, Lin et al investigated the role of TWIST1 and TWIST2 in MACC1-induced VM in gastric cancer. They found that high VM density was significantly correlated with shorter overall survival. Moreover, overexpression of MACC1 upregulated TWIST1/2 expression and induced typical VM in gastric cancer. Thus, these results indicated that MACC1 enhanced the transcriptional level of TWIST1/2, promoted VM in gastric cancer so that facilitated metastasis by increasing blood supply for tumor growth.

MACC1 promotes lymphangiogenesis

Lymph nodes are the first metastasis destination for several cancer types [34], and lymphangiogenesis is the most critical step of lymph node metastasis [35]. In order to explore effective targets of lymphangiogenesis, Sun et al [36] investigated the potential role of MACC1 in lymphangiogenesis and the underlying mechanism. They found that MACC1 was positively correlated with lymphangiogenesis in the clinical samples of gastric cancer patients. An indirect co-culture system was used to determine the role of MACC1 in lymphangiogenesis. The conditional medium from MACC1 overexpressed gastric cancer cells was collected, and found that this condition medium accelerated the capability of tube-like formation of human lymphatic endothelial cells through enhancing cell proliferation and migration. Furthermore, xenografts mice model showed that elevated MACC1 promoted more lymphatic vessels. The potential mechanism was clarified that MACC1 dramatically increased the expression of VEGF-C/VEGF-D in vitro and *in vivo*.

MACC1 and drug resistance

MACC1 promotes Warburg effect and enhances cell resistance to apoptosis

Metabolic stress usually was caused by the requirement of large supply of energy for survival in cancer cells [37]. Thus, glycometabolism is reprogrammed to accommodate the increased energy demand in cancer cells, this metabolic shift was known as the Warburg effect [38]. Lin et al [14] proved that MACC1 expression was positively correlated with the maximum standardized uptake value of ^{18}F-deoxyglucose in gastric cancer patients, and MACC1 enhanced ^{18}F-deoxyglucose uptake *in vitro* and *in vivo*. The underlying mechanism was that MACC1 promotes Warburg effect by enhancing the expressions and activities of a series of glycolytic enzymes, including hexokinase (HK), pyruvate dehydrogenase kinase (PDK) and lactate dehydrogenase (LDH) in gastric cancer cells. This metabolic shift increased cell viability and resistance to apoptosis.

MACC1 enhances drug resistance by promoting Warburg effect

Warburg effect was involved in drug resistance to trastuzumab [39, 40], a humanized antibody targeting HER2 showed strong therapeutic efficacy against HER2-positive gastric cancer [41]. Lin et al [15] found that MACC1 was overexpressed in trastuzumab-resistant cell lines. In addition, elevated MACC1 induced trastuzumab resistant by enhancing Warburg effect *in vitro* and *in vivo*. In regards to the underlying mechanism, MACC1 promoted Warburg effect mainly through activating PI3K/Akt signaling pathway.

MACC1 mediates chemotherapy sensitivity by upregualting MCT1 expression

Chemotherapeutic resistance is a main obstacle for effective treatment of cancer. MACC1 and monocarboxylate 1 (MCT1), a plasma membrane protein co-transporting lactate and H^+, were closely correlated with drug resistance [42]. Wang et al [43] MACC1 and MCT1 were both highly expressed in gastric cancer and exhibited a positive correlation in clinical samples. Moreover, MACC1 was demonstrated to mediate sensitivity of 5-FU and cisplatin in gastric cancer cells. A MCT1 inhibitor AZD-3965 rescued the sensitivity of 5-FU and cisplatin in gastric cancer cells which overexpressed MACC1. Thus, the authors suggested that MACC1 influence the chemotherapy sensitivity by regulating MCT1 expression. This is also a new strategy for overcoming drug resistance.

The diagnostic and prognostic value of MACC1

Hitherto, numerous researches showed that MACC1 is a remarkable biomarker for cancer diagnosis and prognosis in colorectal cancer [44, 45], gastric cancer [30], pancreatic cancer [46], hepatocellular cancer [47], lung cancer [10], ovarian cancer [48], breast cancer [12] and other types of solid cancer (**Table 1**) [25, 49-52].

Table 1. Correlation of MACC1 to clinical parameters in solid cancers (selected references)

Tumor entity	Samples	Number	Method	Correlation to clinical parameters (Kaplan-Meier survival analysis and Cox regression model)	Refs
Colorectal cancer	Tumors, metastases	Male 57 Female 56	qRT-PCR	Metastasis, disease free survival	[4]
	Liver metastasis samples	Male 52 Female 12	qRT-PCR	Metastatic recurrence	[42]
	Blood	Male 200 Female 112	qRT-PCR	Distant metastases, overall survival	[43]
	Tumors, adjacent non-tumors	Male 99 Female 75	qRT-PCR	Tumor invasion, overall survival, disease free survival	[51]
	Tumors	Male 79 Female 75	PCR, sequencing	Overall survival for younger colon cancer patients in early stages	[52]
	Tumors	Male 177 Female 144	PCR, sequencing	Overall survival	[53]
Gastric cancer	Plasma	Male 57 Female 19	qRT-PCR	Overall survival	[54]
Breast cancer	Serum	Female 378	ELISA	TNM stage, tumor size, lymph node metastasis, Ki-67 status, disease free survival	[10]
Lung cancer	Tumors	Male 77 Female 69	qRT-PCR	Recurrence, Disease-free survival	[55]
	Tumors	Male 107 Female 90	IHC	Recurrence, Disease-free survival	[56]
	Plasma	Male 142 Female 130	qRT-PCR	TNM stage, lymph node metastasis, overall survival, disease free survival	[57]
Hepatocellular cancer	-	1293	Meta-analysis	Overall survival, disease free survival, AFP level, tumor number, differentiation, TNM stage, vascular invasion, capsule invasion, metastasis	[45]
Pancreatic cancer	Blood serum	Male 40 Female 20	ELISA	Lymph node metastasis, distant metastasis and a later TNM stage	[44]
Ovarian cancer	Tumors	Female 207	IHC	Tumor/lymph node/metastasis (LNM) grade, implantation, FIGO stage, overall survival	[50]
Renal cancer	Tumors	Male 77 Female 35	IHC	T stage, metastasis, overall survival, disease free survival	[48]
Cervical cancer	Tumors, adjacent non-tumors	Female 181	qRT-PCR, IHC	FIGO stage, pelvic lymph node metastasis, recurrence, overall survival, progression-free survival	[49]

Abbreviations: TNM, tumor, node, metastases; FIGO, International Federation of Gynecology and Obstetric; ELISA, enzyme linked immunosorbent assay.

Colorectal cancer

The diagnostic and prognostic value of MACC1 protein were determined by Stein et al in colorectal cancer [6]. *MACC1* mRNA expression has been identified to predict recurrence of the colorectal cancer [53]. Generation of MACC1-based risk classes was capable of successfully separating patients into poor and good prognosis subgroups. Another study assessed the mRNA level of MACC1 in 174 patients who underwent curative surgery for colorectal cancer, and revealed that high MACC1 expression levels were more susceptible to distant metastases and a poor prognosis [44]. Conversely, patients exhibiting low MACC1 expression showed improved overall survival and disease-free survival than those with high expression. The association between genetic polymorphisms of *MACC1* gene and prognosis in colorectal cancer has also been analyzed. Schmid et al [54] sequenced the coding exons of MACC1 in 154 colorectal tumors and found that the identification of coding MACC1 SNPs in primary colorectal tumors does not improve the prediction for poor outcome of patients. However, Lang et al [55] isolated the genomic DNA from 318 specimens of colorectal cancer patients and identified the most common variants of MACC1 locus. They revealed that SNP rs1990172 as a predictor for shorter overall survival in colorectal cancer. These studies indicated that MACC1 was a promising diagnostic and prognostic value of MACC1 in colorectal cancer.

Gastric cancer

Recently, Stein et al [4] conducted a prospective study in gastric cancer to explore the diag-

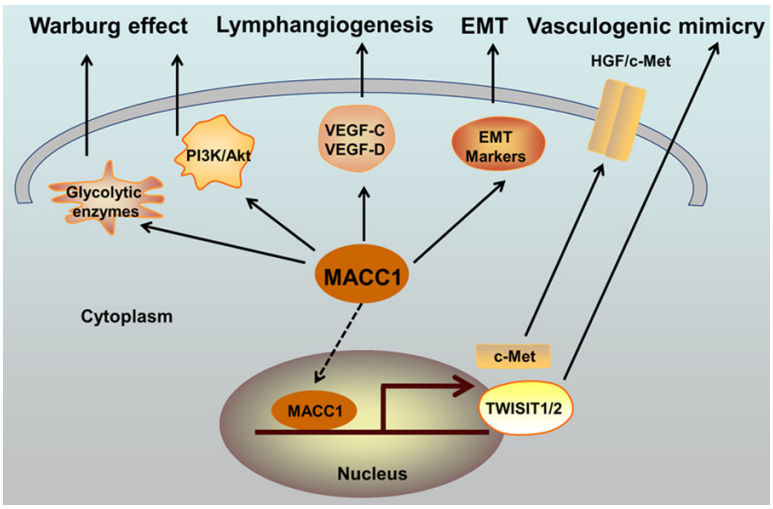

Figure 1. MACC1 participates in multiple biological processes in cancer cells and induces metastasis and drug resistance.

nostic and prognostic value of circulating MACC1. Based on the blood assay for transcript quantification of MACC1, the author found that levels of circulating MACC1 in plasma were increased in gastric cancer patients of each disease stage. Gastric cancer patients with high circulating MACC1 transcripts levels in plasma demonstrated significantly shorter survival when compared with patients demonstrating low MACC1 levels. This study showed that levels of circulating MACC1 transcripts in plasma for gastric cancer patients are of diagnostic value and are prognostic for patient survival.

Breast cancer

Tan et al [5] also determine the diagnostic and prognostic value of preoperative serum MACC1 levels in breast cancer. Using ELISA assay, they measured the serum MACC1 levels in 378 breast cancer patients, 120 patients with benign disease, and 40 healthy volunteers. The results showed that serum MACC1 were higher in breast cancer patients than patients with benign disease or healthy volunteers. Moreover, serum MACC1 level successfully discriminated breast cancer patients from normal and healthy control with a strong sensitivity and specificity. Meanwhile, serum MACC1 exhibited significant prognostic value in breast cancer. High MACC1 level was correlated with shorter disease-free survival. Thus, this study demonstrated that circulating MACC1 could serve as a promising diagnostic and prognostic biomarker for breast cancer.

Lung cancer

The diagnostic and prognostic value of MACC1 in lung cancer has been determined by several studies. Shimokawa et al [56] clarified the role and the clinical significance of MACC1 mRNA level in resected stage I non-small cell lung cancers (NSCLC). Gu et al [57] analyzed the MACC1 protein level in 197 patients who underwent a complete resection for NSCLC by immunohistochemical (IHC) staining. The result from these two studies showed that both the mRNA level and protein level of MACC1 was associated with a poor survival in patients with NSCLC, and indicated that MACC1 was a useful marker for predicting postoperative recurrence in patients with NSCLC. Recently, the value of circulating MACC1 was explored by reverse transcription quantitative real-time polymerase chain reaction [58]. Plasma MACC1 mRNA level was highly expressed in NSCLC patients than in patients with benign disease or in healthy volunteers. The diagnostic capability of circulating MACC1 mRNA was higher than that of carcinoembryonic antigen or cytokeratin-19. Furthermore, high MACC1 expression was correlated with poor overall survival and disease-free survival in NSCLC. These studies indicated that MACC1 is a strong diagnostic and prognostic marker in lung cancer.

Hepatocellular cancer

Both the mRNA level and the protein level of MACC1 were higher in hepatocellular cancer tissues than normal tissues [59-61]. Recently, Sun et al [47] conducted a meta-analysis which included 9 studies with a total 1293 hepatocellular cancer patients. The result showed that overexpression of MACC1 was correlated with poor overall survival and diseases free survival. MACC1 can serve as an diagnostic and prognostic value of MACC1 in hepatocellular cancer.

Conclusion

Taken together, we conclude that MACC1 participates in multiple biological processes in cancer cells and induces metastasis and drug resistance (**Figure 1**). MACC1 served as a transcription factor to increase MET promoter activity, so that MACC1 promoted metastasis in multiple types of cancer through the HGF/c-Met signaling pathway. EMT process is one of the critical step in cancer invasion and metastasis, by which cancer cells lose their epithelial phenotype and cell-cell adhesion and gain invasion mesenchymal properties. MACC1 facilitated metastasis by upregulating EMT associated makers or signaling pathway, such as fibronectin, MMP2, MMP9, vimentin and Wnt/β-catenin pathway. In fact, lymphangiogenesis is the core process of lymph node metastasis, and VM formation contributes to the blood supply necessary for tumor growth and metastasis. MACC1 was confirmed that accelerated these processes and resulted in metastasis. Additionally, MACC1 induced metabolic shift and enhancing drug resistance in several cancer types. Meanwhile, numerous researches showed that MACC1 is a remarkable biomarker for cancer prognosis in multiple types of cancer. As MACC1 participating in multiple biological processes both in metastasis and drug resistance, as well as MACC1 was correlated with multiple types of cancer prognosis, MACC1 is a promising therapeutic target for intervention strategies toward prevention and restriction of tumor metastasis and drug resistance.

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Disclosure of conflict of interest

None.

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