Minireview

Overexpression of MACC1 leads to downstream activation of HGF/MET and potentiates metastasis and recurrence of colorectal cancer

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Abstract

Survival rates from colorectal cancer (CRC) differ dramatically according to the stage of the tumor at diagnosis, with survival rates of 90% for patients with stage I disease but only 49% for those with stage III cancer. Many serum and tumor markers have been identified but none has provided a significant improvement over tumor stage as a prognostic indicator for cancer recurrence for patients with stage II or III disease. Aberrant activation of the hepatocyte growth factor (HGF)/HGF receptor (MET) signaling pathway is associated with both malignant transformation and metastatic potential of CRC. MACC1 (metastasis-associated in colon cancer-1) is a newly discovered gene that regulates this signaling cascade. The significant correlation between overexpression of MACC1 in CRC and both malignant transformation and subsequent risk for metastases in stage II and III CRC indicates that MACC1 tumor typing may prove valuable for determining risk for CRC recurrence. MACC1 may also be an important therapeutic target for CRC treatment.

Detection of colorectal cancer recurrence

To date, the most reliable prognostic indicator for colorectal cancer (CRC) has been stage, but discerning which of those patients with stage II or III disease will be among the 25-51% of cases to develop recurrent cancer and succumb to the disease remains one of the most problematic and frustrating issues concerning clinical care and cancer surveillance strategies for CRC patients. Recent guidelines by the European Group of Tumor Markers for the clinical use of CRC markers determined that currently only measurement of serum carcinoembryonic antigen (CEA) every two to three months may be of value for recognizing recurrence in patients with stage II or III disease [1]. Other serum markers, including cancer antigen CA19-9, CA242 and tissue inhibitor of metalloproteinases (TIMP-1), or the tumor markers thymidylate synthase, microsatellite instability, p53, K-ras, and deleted in colon cancer (DCC) offer no advantage beyond the limited specificity and sensitivity of CEA for early detection of cancer recurrence [1]. Stein et al. [2] report the association of overexpression of MACC1 with an increased risk for CRC metastasis, providing compelling data that this gene may be useful both as a prognostic marker and possibly as a chemopreventive or therapeutic target.

Hepatocyte growth factor (HGF) and the HGF receptor (MET)

MACC1 is located on chromosome 7p21.1 and regulates injury response and tissue growth via the HGF/MET signaling pathway. Of note, HGF and MET also map to chromosome 7 (7q21.1 and 7q31, respectively). Polysomy of chromosome 7 is a common finding in both glioblastomas and CRC tumors [3], and recent genome-wide analysis of siblings with familial CRC not related to known genetic conditions implicated 7q31 as a region linked to hereditary CRC [4].
HGF regulates growth of liver sinusoidal endothelial cells and interacts with interleukin 7 to regulate the immune response to mucosal lymphocytes in the intestinal mucosa [5], mainly via activity in the stroma. The malaria parasite Plasmodium sporozoite stimulates stromal cell secretion of HGF, which activates its receptor MET. Activation of HGF/MET in turn disrupts the host-cell cytoskeleton, making the hepatocytes vulnerable to infection with this parasite [6]. HGF prompts tumor invasiveness via tumor-stromal cell interactions. Increased stromal expression of HGF is associated with many cancer types, including endometrial and breast cancer [7,8].

MET is a proto-oncogene considered essential for metastatic potential in CRC [9-12]. MET was first recognized as an oncogene in osteosarcoma cell lines [13], and later Schmidt et al. [14] detected missense mutations in the tyrosine kinase domain of MET both in the germline of individuals with hereditary papillary renal carcinoma and in somatic DNA from sporadic papillary renal carcinomas. MET is expressed mainly on the surface of epithelial cells. Missense mutations in the tyrosine kinase domain of MET also have been detected in childhood hepatocellular carcinomas [15]. MET encodes the tyrosine kinase that serves as a cell surface receptor for HGF/scatter factor (HGF/SF), which is one member of a family of soluble proteins known as scatter factors that regulate invasive growth [16,17].

**Activation of HGF/MET signaling can lead to invasive growth and cancer**

Aberrant activation of MET deregulates the HGF/MET signaling pathway, leading to increased cell proliferation, invasion and metastasis [18]. MET has multiple docking sites, including a transducer docking site that intensifies both the transforming and metastatic abilities of this oncogene. HGF binding to MET leads to phosphorylation of two tyrosine residues in the carboxyl terminus, which, once phosphorylated, can recruit the adapter proteins Gab1, Grb2, and Shc and the p85 subunit of phosphatidylinositol-3-kinase (PI3K) [19]. MET then activates downstream signaling of the Ras-mitogen-activated protein kinase (MAPK) and/or PI3K-Akt pathways to promote the invasive growth characteristic of malignancies and their metastatic properties. However, MET can be activated independently of HGF binding through amplification and/or mutation. A single point mutation in the transducer docking site results in inhibition of the metastasis function of this signaling cascade, while preserving its oncogenic transformation capacity [20].

**MACC1 is a reliable prognostic indicator and new target for treatment of CRC**

Although the cellular distribution of MET is a strong prognostic indicator for survival from colon [27] and breast cancer [28,29], assays of expression of MET have not been routinely used for clinical purposes to predict which patients have the highest risk for CRC recurrence. The results reported by Stein et al. suggest that MACC1 mRNA expression is an independent prognostic indicator of recurrence
and disease-free survival that may outperform that of MET. Patients with CRC tumors with low MACC1 mRNA had 5-year survival rates of 80% compared to 15% for those with high levels of MACC1 mRNA expression [2].

MACC1 mRNA expression may be used in the future for prognostication and guidance in determining which patients might most benefit from standard chemotherapeutic strategies. If MACC1 overexpression is found to be detectable in serum, stool or urine, it could serve as a marker of recurrence following CRC surgery and treatment. In addition, MACC1 inhibitors may be developed to disrupt aberrant signaling of HGF/MET, thus minimizing tumor invasion and metastasis and providing benefits to CRC patients at both the chemopreventive and therapeutic levels.

**Abbreviations**

CA, cancer antigen; CEA, carcinoembryonic antigen; CRC, colorectal cancer; DCC, deleted in colon cancer; EGFR, enhanced transforming growth factor-α; HGF, hepatocyte growth factor; MET, HGF receptor proto-oncogene; AMG102, humanized anti-HGF antibody; MACC1, metastasis-associated in colon cancer-1; MAPK, mitogen-activated protein kinase; SF, scatter factor; TIMP-1, metastasis-associated in colorectal cancer; Oncology 1999, 56:314-321.

**Competing interests**

The author declares that she has no competing interests.

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