

Clinical impacts of mesothelin expression in gastrointestinal carcinomas

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Abstract

Mesothelin, C-ERC/mesothelin is a 40-kDa cell surface glycoprotein that is normally present on normal mesothelial cells lining the pleura, peritoneum, and pericardium. Moreover, mesothelin has been shown to be overexpressed in several human cancers, including virtually all mesothelioma and pancreatic cancer, approximately 70% of ovarian cancer and extra bile duct cancer, and 50% of lung adenocarcinomas and gastric cancer. The full-length human mesothelin gene encodes the primary product, a 71-kDa precursor protein. The 71-kDa mesothelin precursor is cleaved into two products, 40-kDa C-terminal fragment that remains membrane-bound *via* glycosylphosphatidylinositol anchor, and a 31-kDa N-terminal fragment, megakaryocyte potentiating factor, which is secreted into the blood. The biological functions of mesothelin remain largely unknown. However, results of recent studies have suggested that the mesothelin may play a role of cell proliferation and migration. In pancreatic cancer, mesothelin expression was immunohistochemically observed in all cases, but absent in normal pancreas and in chronic pancreatitis. Furthermore, the expression of mesothelin was correlated with a poorer patient outcome in several human cancers. The limited mesothelin expression in normal tissues and high expression in many cancers makes it an attractive candidate for cancer therapy. The present review discusses the expression and function of mesothelin in cancer cells and the utility of mesothelin as

a target of cancer therapy.

Key words: Mesothelin; Luminal membrane expression; Cytoplasmic expression; Tumor marker; Cancer therapy

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Core tip: Mesothelin is a 40-kDa cell surface glycoprotein expressed on normal mesothelial cells lining the pleura, pericardium, and peritoneum. Moreover, mesothelin has been shown to be overexpressed in several cancer types. Recent studies have suggested that the overexpression of mesothelin increases cell proliferation and migration. Furthermore, the expression of mesothelin was related to an unfavourable patient outcome in several human cancers. The limited mesothelin expression in normal tissues and high expression in many cancers makes it an attractive candidate for cancer therapy.

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INTRODUCTION

Mesothelin is a 40-kDa cell surface glycoprotein that is normally present on normal mesothelial cells lining the pleura, peritoneum, and pericardium^[1,2]. Moreover, mesothelin has been shown to be overexpressed in several human cancers, including virtually all mesothelioma and pancreatic cancer, approximately 70% of ovarian cancer and extra bile duct cancer, and 50% of lung adenocarcinomas and gastric cancer^[3-6] (Table 1). The full-length human mesothelin gene (Full-ERC/mesothelin) encodes a 71-kDa precursor protein. The 71-kDa mesothelin precursor is cleaved into two products, 40-kDa C-terminal fragment (C-ERC/mesothelin) that remains membrane-bound *via* glycosylphosphatidylinositol anchor^[7], and a 31-kDa N-terminal fragment (N-ERC/mesothelin, megakaryocyte potentiating factor), which is secreted into the blood (Figure 1)^[1]. The function of mesothelin in cancer is still unclear. However, results of recent studies have suggested that the mesothelin may play a role of tumor progression *in vitro*^[8-11] and *in vivo*^[11,12].

MESOTHELIN EXPRESSION IN GASTROINTESTINAL CANCERS

Co-expression of mesothelin and CA125 correlates with unfavorable patient outcome in pancreatic ductal adenocarcinoma

Mesothelin could play a role of the binding to CA125^[13-15].

Mesothelin and CA125 binding may be important in the peritoneal spread^[13,15]. In ovarian cancer, advanced clinical stage and/or high histological grade patients showed mesothelin expression and CA125 expressions^[15]. Our group showed that the co-expression of mesothelin and CA125 group was a higher histological grade and a higher level of blood vessel permeation and correlated with recurrence rate and poor patient outcome in pancreatic ductal adenocarcinoma^[16]. These findings suggest that the co-expression of mesothelin and CA125 may lead to tumor development, metastasis, and a poorer patient prognosis.

Luminal membrane expression of mesothelin is a prominent poor prognostic factor

The expression of mesothelin was related to an unfavorable patient outcome in pancreatic ductal adenocarcinoma^[16,17]. Our group investigated mesothelin expression in gastric cancers by using immunohistochemistry, especially focusing on the localization of mesothelin, *i.e.*, "luminal membrane-positive" and/or "cytoplasm-positive" (Figure 2)^[18].

The overall survival revealed that the "luminal membrane-positive" group showed a significantly poorer outcome compared to the "luminal membrane-negative" group. On the other hand, the "mesothelin-positive" group and the "cytoplasmic-positive" group were not correlated with overall survival in the gastric cancer patients.

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas has a histological spectrum ranging from benign adenoma to invasive cancer. We performed an immunohistochemical analysis of mesothelin expression in IPMN. Mesothelin was absent in all of the normal pancreatic tissues. But, mesothelin was expressed in both adenoma and carcinoma cells. Most of mesothelin expressed adenoma cells exhibited slight "cytoplasmic-positive", and the "luminal membrane-positive" group has a tendency of poor prognosis and high recurrence rate^[19].

Based on these results, the "luminal membrane-positive" of mesothelin is a useful prognostic factor, implying that membrane-localized mesothelin might have the significant function of the aggressive behavior in the cancer cells.

THE ROLE OF MESOTHELIN EXPRESSION IN TUMOR BIOLOGY

Our study generated the novel finding, the potential role of the "luminal membrane-positive" mesothelin in the malignant behavior of tumor cells^[18-21]. The human mesothelin gene encodes a 71-kDa precursor protein (Full-ERC/mesothelin). This precursor protein is cleaved by furin-like proteases into a 31-kDa N-terminal secreted form (N-ERC/mesothelin) and a C-terminal fragment, 40-kDa mesothelin (C-ERC/mesothelin)^[1,7,22]. The 5B2 anti-mesothelin antibody, which we used in our studies,

Table 1 Mesothelin expression in human cancer detected by immunohistochemistry

Tumour	Mesothelin expressions (%)	Comments	Ref.
Pancreatic cancer	86-100	Co-expression of mesothelin and CA125 group associated with a poorer patient prognosis	[6,16,17]
Gastric cancer	29-59	Luminal membrane expression is one of the poor prognostic factors	[6,18,27,35]
Extrahepatic bile duct cancer	72-100	Luminal membrane expression or cytoplasmic expression of mesothelin could be a reliable prognostic factor	[6,21]
Colorectal cancer	28-58	Luminal membrane expression was associated with lymphatic invasion	[6,20]
Intraductal papillary mucinous neoplasm	57	Luminal membrane expression was correlated with the histological classification of the tumor and the recurrence rate	[19]

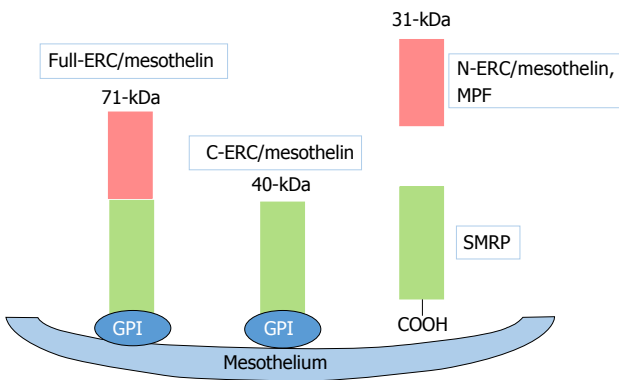


Figure 1 Schematics showing the maturation of mesothelin protein. The primary product of the full-ERC/mesothelin gene is a 71-kDa precursor protein. This protein is physiologically cleaved, releasing a 31-kDa fragment, N-ERC/mesothelin, into the blood. MPF: Megakaryocyte potentiating factor; SMRP: Soluble mesothelin-related peptide; GPI: Glycosylphosphatidylinositol.

can detect the 71-kDa precursor protein (Full-ERC/mesothelin) and the 40-kDa C-terminal fragment (C-ERC/mesothelin), but not the 30-kDa N-terminal fragment (N-ERC/mesothelin). Based on the specificity of this antibody, the “luminal membrane-positive” mesothelin observed in our study might have indicated the existence of 40-kDa mesothelin (C-ERC/mesothelin) membrane-bound form, while the “cytoplasmic-positive” mesothelin might have indicated the presence of the the 71-kDa precursor protein (Full-ERC/mesothelin). To demonstrate the mechanism of the membranous localization of mesothelin, we enforced the expression of Full-, C-, and N-ERC/mesothelin in human colorectal cancer (CRC) cell lines^[20]. The 7E7 antibody, which recognizes the 30-kDa N-terminal fragment (N-ERC/mesothelin), revealed the diffuse cytoplasmic expression of Full- and N-ERC/mesothelin in Full-WiDr and N-WiDr. In contrast, the 22A31 antibody, which recognizes 40-kDa mesothelin (C-ERC/mesothelin), demonstrated a dot-like expression of Full- and C-ERC/mesothelin in Full-WiDr and C-WiDr. Moreover, some of the dot-like spots along with the cellular membrane were merged with actin, showing yellow signals. According to these results, we confirmed the membranous expressions of C-ERC/mesothelin in CRC cell lines.

To demonstrate the biological role of Full-, C-, and N-ERC/mesothelin in the lymphatic invasion of CRC, we performed an *in vitro* lymphatic invasion assay. C-ERC/

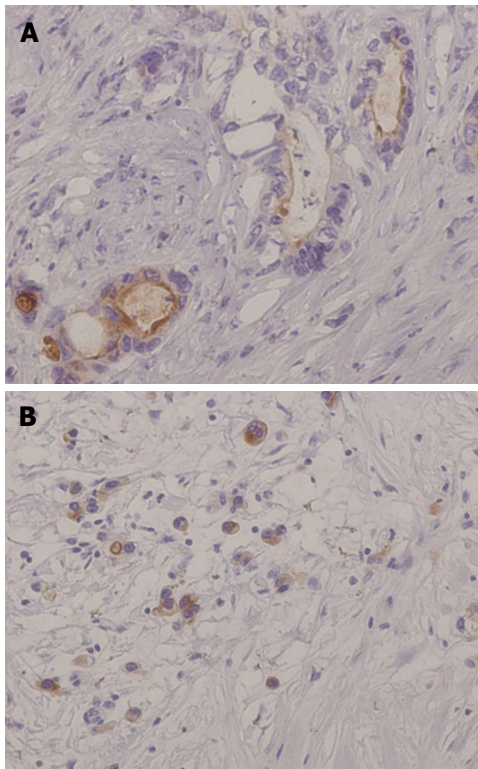


Figure 2 The expression of mesothelin in gastric cancer. A: Luminal membrane expression. The entire circumference of the cell membrane was stained; B: “Cytoplasmic expression” with granular cytoplasmic staining in cancer cells.

mesothelin, the 40-kDa membrane-localized fragment, promoted the lymphatic invasion by increasing cell adhesion to lymphatic endothelial cells.

THE PATHWAYS OF MESOTHELIN INVOLVED IN CANCER

Recent studies reported that mesothelin is not only associated with increased cell proliferation and the migration of pancreatic cancer cells *in vitro*^[11,23], but also contributes to tumor progression *in vivo*^[11]. Mesothelin protects cancer cells from paclitaxel-induced apoptosis through both the concomitant activation of PI3K/Akt and MAPK/ERK pathways^[24]. Overexpression of mesothelin in pancreatic cancer cells leads to constitutive activation of signal transducer and activator of transcription 3, which results in enhanced expression of cyclin E and cyclin

E/cyclin-dependent kinase 2 complex formation as well as increased G1-S transition^[23]. Mesothelin expression correlated closely with interleukin (IL)-6 in human pancreatic cancer specimens and cell lines. Cancer cell with forced mesothelin expression grow faster than control cells by producing higher quantities of IL-6^[9,10].

BLOOD TEST FOR MESOTHELIN

Several ELISAs have been developed to measure the levels of soluble mesothelin-related peptide (SMRP) and megakaryocyte potentiating factor (MPF, N-ERC/mesothelin). The soluble form of mesothelin is likely due to an abnormal splicing event resulting in a frameshift mutation and premature termination at amino acid 600 deleting the amino acids at the COOH terminus that are responsible for its association with the cell membrane. The full-length human mesothelin gene encodes the primary product, a 71-kDa precursor protein. It can be physiologically cleaved by some furin-like proteases into a 40-kDa C-terminal fragment that remains membrane-bound, and a 31-kDa N-terminal fragment, which is secreted into the blood. The C-terminal 40-kDa fragment is referred to as mesothelin. In contrast, the N-terminal 31-kDa fragment is a secreted protein identified as MPF. SMRP has proven to be a promising cancer biomarker in the sera of patients with tumors of mesothelial origin^[25,26]. MPF has been reported to be expressed in gastrointestinal cancers^[27,28].

Wu *et al.*^[29] revealed that SMRP performs better than CA125 as a tumor marker for epithelial ovarian cancer, it increases only in malignant patients and not in benign patients or healthy volunteers. Furthermore, the sensitivity is enhanced when combined with CA125. Hassan *et al.*^[30] identified a positive correlation with the tumor burden and SMRP levels, as a marker for monitoring the response to treatment of malignant mesothelioma.

MESOTHELIN TARGET IMMUNOTHERAPY

Because of the high expression of mesothelin in many malignancies and its limited expression in normal tissues, mesothelin has been suggested as an attractive target for immunotherapy. Several therapeutic agents that target mesothelin have been developed and some are being evaluated in preclinical and clinical studies. SS1P is an immunotoxin being clinically tested as a systemic agent in solid tumor patients. Two phase I trials of single-agent SS1P have been performed^[31,32]. The majority of patients developed antidrug antibodies by the end of their first cycle, resulting in non-therapeutic drug levels if any additional cycles were given. MORAb-009 (amatuximab) is a chimeric antibody. A phase I clinical trial of MORAb-009 for mesothelioma, pancreatic cancer, and ovarian cancer patients has been completed^[33]. Eleven of 24 subjects had stable disease. Phase II studies of MORAb-009 in different mesothelin-expressing cancers are ongoing. The mesothelin tumor vaccine in clinical development

is CRS-207. The safety of this vaccine was established in a phase I clinical trial of patients with mesothelin-expressing refractory cancers^[34].

CONCLUSION

Mesothelin is an attractive antigen that is expressed in several gastrointestinal cancers. Recent studies have revealed oncogenic functions of mesothelin in cancer proliferation and invasion and drug resistance. Also, soluble mesothelin could be useful as a tumor marker. The limited mesothelin expression in normal tissues and high expression in many cancers makes it an attractive candidate for cancer therapy.

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