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Prognostic significance of soluble major histocompatibility complex class I-related chain A (sMICA) in gastric cancer

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The major histocompatibility complex class I-related chain genes A and B (*MICA* and *MICB*, present at 6p21.33) encode cell surface transmembrane glycoproteins related to those of the HLA system, and which are recognised by those NK cells, γ/T cells and $CD8^+$ T cells that express NKG2D [1]. The enforced expression of NKG2D ligands on transplantable murine tumours elicits immune rejection by NK cells, $CD8^+$ T lymphocytes and perforin, whilst administration of blocking antibodies to NKG2D enhances tumour susceptibility. Nonetheless, the constitutive expression of MICA on human tumours promotes ligand shedding, which triggers internalisation of surface NKG2D, impaired NK cell and $CD8^+$ T lymphocyte function, and expansion of an unusual population of $NKG2D^+CD4^+$ T cells with regulatory properties [2,3]. MICA expression in normal tissues is restricted to the thymic epithelium and scattered cells in the gastrointestinal mucosa, but is commonly detected on solid and haematological malignancies [4]. Surface MICA/B forms a complex with a disulphide isomerase/chaperone that induces a conformational change, enabling proteolytic cleavage of MICA/B by a disintegrin and metalloproteinase protein [5].

A soluble isoform of MICA/B (sMICA/B) is present in the circulation and may be bioactive *in vivo*. The interaction of sMICA/B with NKG2D results in the endocytosis and degradation of receptor–ligand complexes, and also suppresses NKG2D-mediated host cancer rejection [6]. The shedding of sMICA/B by human tumours not only hinders recognition of the MICA/B-expressing tumour cells but also leads to down-regulation of NKG2D expression on circulating CD8 T cells, NK cells and γδT cells, so that the antitumour immune response is impaired [7]. Indeed, high levels of sMICA molecules are strongly linked with poor clinical outcome in patients with various types of cancer [5]. High tumour MICA/B expression is associated with unfavourable outcomes in ovarian cancer, non-small-cell lung carcinoma and breast cancer [8]. However, in patients with high MICA-expressing gastric cancer tumours, the median disease-free survival (DFS) and overall survival (OS) are longer than for patients whose tumours express little MICA. In a multivariate analysis, stage and MICA expression were independent prognostic factors for DFS and OS [9].

Gastric cancer is one of the leading causes of cancer-related mortality worldwide. Although recent advancement in gastric cancer early detection, therapy and prevention partly enhanced survival rate of early gastric cancer, Stage IV gastric cancer is still incurable with a very poor 5-year survival rate of approximately 4–5% [10]. The curative procedure of gastric cancer is unsatisfactory because the early gastric cancer is difficulty to discover in a purely clinical setting, and there are no sufficiently specific or sensitive laboratory markers of this malignancy. Therefore, the pre-selection of high-risk individuals with a simple and effective non-invasive biomarker, prior to endoscopic examination, could have a role in gastric cancer mass screening. We hypothesised high levels of sMICA in gastric cancer that are linked to clinicopathological features and which predict a poor outcome.

From March 2008 to January 2013, 196 patients (with histologically confirmed gastric carcinomas from surgically resected tissues) attending the Affiliated Hospital of Qingdao University were enrolled. Exclusion criteria were other carcinomas, inflammatory disease and autoimmune disease (wherein sMICA levels are elevated [11]). Histopathology was evaluated by independent pathologists who were blinded to the clinical details of the patients. Tumour node metastasis (TNM) stage was defined according to the 7th edition of American Joint Committee on Cancer staging system. Serum from 46 healthy individuals and 74 patients without gastric cancer (but with minimal gastritis [$n = 41$], gastric ulcers [$n = 7$] or normal appearance of the gastric mucosa on gastroscopic examination [$n = 26$]) was also obtained. Clinicopathologic characteristics were obtained, and survival analyses were conducted for the 146 patients who were followed up for at least 5 years. This study conformed to the ethical guidelines of the Declaration of Helsinki and has been approved by the Institutional Review Board of the Affiliated Hospital of Qingdao

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University, China. Written informed consent, as required by the institutional review board, was obtained from all subjects.

Venous blood was collected into plain tubes during hospitalisation before the patients underwent operations. Serum sMICA was measured by sandwich ELISA (R&D Systems, Hangzhou, China). Data were analysed on SPSS Version 22.0 for Windows. Continuously variable data are presented as mean (SD) and analysed by *t*-test and ANOVA, categorical as number/percent and analysed by chi-squared testing. Relationships between sMICA and each of the clinicopathological parameters were analysed using the Mann–Whitney test. Overall survival was calculated from the date of surgery, and only deaths due to gastric cancer were considered. As there was no clinically defined cutoff point for serum sMICA level, the median was used to divide the patients into two groups (low vs. high serum sMICA level). Survival durations were calculated via the Kaplan–Meier method. The log-rank test was employed to compare the cumulative survival rate and time to progression in the patient groups. $P < 0.05$ was considered statistically significant.

The mean (SD) age of patients was 59.6 (10.3) years and that of the control individuals was 58.3 (10.6) years ($P = 0.453$). The patient group was 132 were men and 64 women, the control group 62 men and 28 women ($P = 0.264$). The sMICA level in healthy controls was 16.4 (3.6) ng/mL. In patients with minimal gastritis, it was 17.7 (3.8) ng/mL, gastric ulcers 15.8 (3.8) ng/mL, and normal appearance of the gastric mucosa on gastroscopic examination 16.7 (3.6) ng/mL ($P = 0.284$). sMICA levels of the 196 patients with gastric cancer were 254.6 (68.7) ng/mL versus 16.7 (3.7) ng/mL in the combined control group ($P = 0.001$). On ROC analysis, a sMICA level cutoff value of 92 ng/mL provided the best discrimination between gastric cancer patients and controls, with an AUC of 0.83 (95% confidence interval 0.75–0.89) ($P < 0.001$). The sensitivity, specificity and accuracy for predicting gastric cancer were 81.4%, 63.6% and 75.2%, respectively.

Kaplan–Meier survival curves for the 146 patients followed for 5 years are shown in Figure 1. The survival rates for patients with higher sMICA levels (>92 pg/mL) were significantly worse than those with lower levels ($P = 0.008$). On Cox univariate analysis, hepatic metastasis, serosal invasion, lymph node metastasis, lymphatic invasion, TNM stage and sMICA levels were of prognostic significance for poor OS (Table 1). On Cox multivariate analysis with backward stepwise calculation, serosal invasion, lymph node metastasis and (unsurprisingly) TNM stage were independent risk factors for poor survival.

sMICA shows promise as a new biomarker of cancer: it is elevated in association with tumour growth and distant metastasis of prostate cancer [12], non-small-cell lung carcinoma [13] and pancreatic ductal adenocarcinoma [14]. Poor survival of cancer patients linked with a high level of sMICA has also been demonstrated

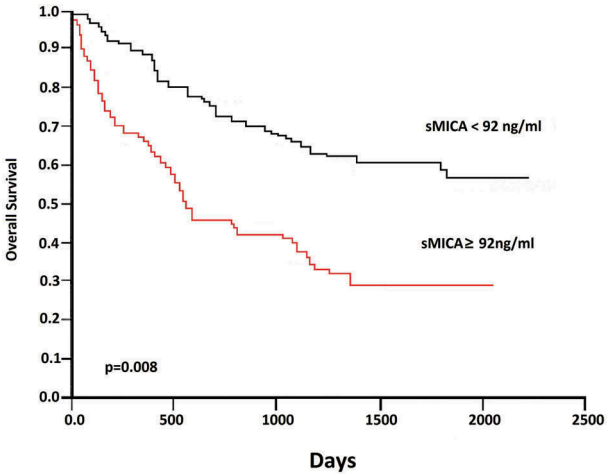

Figure 1. Overall of survival for all gastric cancer patients in relation to sMICA.

Table 1. Univariate and multivariable analysis for the predictors of mortality in gastric cancer patients.

		Univariate analysis		Multivariable analysis	
Groups	(*n*/*n*)	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age ≥ 60 vs. <60	67/129	1.32 (0.95–2.59)	0.143	/	/
Sex: Male vs. female	132/64	1.17 (0.75–2.42)	0.256	/	/
Hepatic metastasis Yes vs. No	21/175	8.94 (4.76–18.5)	0.017	1.57 (0.94–2.89)	0.069
Histological type Differentiated vs. Undifferentiated	112/84	1.32 (0.83–2.26)	0.194	/	/
sMICA (ng/mL) Low vs. high	107/89	2.62 (1.48–8.14)	<0.001	1.87 (0.93–3.84)	0.128
Venous invasion Yes vs. No	38/158	2.79 (1.46–5.35)	0.002	2.14 (1.08–4.21)	0.027
Lymphatic invasion Yes vs. No	77/119	2.09 (1.25–4.26)	0.028	1.86 (1.18–3.94)	0.078
TNM stage I/II vs. III/IV	124/72	5.72 (1.96–16.83)	0.002	5.44 (1.83–14.62)	0.003
Tumour size ≥5cm vs. <5cm	63/133	1.79 (1.03–2.25)	0.147	/	/
Serosal invasion Yes vs. No	69/127	4.56 (1.87–10.5)	0.003	3.28 (1.87–6.37)	0.014
Peritoneal metastases Yes vs. No	60/136	1.14 (0.89–4.67)	0.094	/	/
Lymph node metastasis: Yes vs. no	61/135	3.17 (1.65–8.39)	0.007	2.45 (1.37–4.86)	0.037

n = number in each category.

[12,13]. Ribeiro et al. [15] reported that sMICA expression was significantly higher in the tumour than in normal gastric mucosa. Furthermore, tumours > 5 cm showed significantly higher MICA expression than tumours ≤ 5 cm, and patients presenting tumours > 5 cm that expressed MICA had substantially shorter survival. We extend these data in our study of sMICA in gastric

cancer, examining links with clinical outcome. As with previous reports [11–13], there was significant elevation of sMICA in patients with gastric cancer in comparison with the controls. Furthermore, sMICA level had a significant impact on survival and was an independent predictor of prognosis in univariate analysis. However, this pre-surgical feature lost significance in multivariate analysis to indices discovered after surgery.

We acknowledge a limitation of relatively small numbers overall (and in some sub-analyses) and the possibility that other clinical factors (such as post-surgical treatment) may have influenced outcome. Nevertheless, our data represent an advance in biomedical science because it shows raised sMICA in gastric cancer that predicts outcome, and as such may be the first useful laboratory index in this common malignancy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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