Mesenchymal Stem Cell Marker Expression in Gastric Cancer Stroma

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Abstract. *Background/Aim: Spindle-shaped stromal cells of tumors are derived from various cellular origins, including mesenchymal stem cells (MSCs). MSCs express CD73, CD90 and CD105 antigens. Herein, the aim was to investigate the association between the expression of specific MSC markers in gastric cancer stromal cells and the clinicopathological features of the disease. Materials and Methods: The expression of CD73, CD90 and CD105 in spindle-shaped cancer stromal cells was studied by immunohistochemistry in tissue arrays containing 546 gastric cancer cases. Univariate and multivariate analyses were performed to evaluate the association of MSC marker expression with clinicopathological variables. Results: Spindle-shaped cancer stromal cells expressing the MSC markers CD73, CD90 or CD105 were associated with larger tumor size, advanced cancer, venous infiltration, lymphatic infiltration, and lymph node metastasis. Statistical analysis demonstrated that the presence of CD105-positive spindle cells was an independent prognostic factor of advanced cancer, lymph node metastasis and EBV infection in multivariate analysis. Conclusion: Spindle-shaped gastric cancer stromal cells expressing CD73, CD90 or CD105 are involved in disease progression, and among them, CD105-positive cells are strongly associated with poor prognosis.*

The prognosis of advanced gastric cancer is still poor (1, 2) and identifying the mechanism of cancer progression remains challenging (2). It is well known that interactions between carcinoma cells and the tumor stroma are crucial for tumor growth and progression (3, 4). Among cancer stromal cells, research has largely focused on cancer-associated fibroblasts (CAFs); however, their study is hampered due to the lack of

specific markers to identify CAFs (3). CAFs comprise a heterogeneous population of cells with various origins, including resident fibroblasts, fibrocytes, pericytes, endothelial cells, smooth muscle cells, adipocytes, epithelial cells, bone marrow-derived cell and mesenchymal stem cells (MSCs) (3-5). The latter MSCs seem to play a critical role in cancer progression (6).

Multipotent MSCs are spindle-shaped and are found at perivascular sites in various human tissues and organs (7, 8). MSCs are introduced to a tumor microenvironment by soluble factors released from inflammatory cells or tumor cells (9). MSCs, as defined by the International Society for Cellular Therapy (ISCT), express CD73 (Ecto-5'-nucleotidase), CD90 (Thy-1) and CD105 (Endoglin) (10). Previous cancer studies used MSCs mainly isolated from bone marrow or umbilical cord blood (11-14). MSC-like cells isolated from human gastric cancer stroma (GC-MSCs) were found to possess similar characteristics to bone marrow-derived MSCs (BM-MSCs), including spindle-shaped morphology and MSC immunophenotype (15). However, the two cell populations differed in the number of cytoplasmic organelles and the higher growth ability and long-term proliferation of GC-MSCs compared to BM-MSCs (16). In gastric cancer, MSCs that come in contact with premalignant or malignant epithelial cells enhance growth and promote epithelial to mesenchymal transition, thus promoting cancer development and progression (6); whereas gastric cancer cells can also trigger MSCs to differentiate into CAFs (17).

To our knowledge, this is the first study to investigate the association of the expression of MSC markers with clinicopathological factors in a large number of gastric cancer cases. The expression of CD73, CD90 or CD105 in spindle-shaped gastric cancer stromal cells was assessed, and their association with cancer progression was examined.

Patients and Methods

Tissue arrays. A total of 546 primary gastric cancers from 524 patients surgically resected from 2000 to 2011 were obtained from the archives of the Department of Pathology, Teikyo University

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Hospital, Tokyo, Japan. Some of the gastric cancer cases were included in our previous report (18). This study received approval from the Ethics Committee of the Teikyo University School of Medicine (No. 13-021, 8 May 2013). Formalin-fixed, paraffin-embedded (FFPE) tissue blocks were used for staining. Histopathological data were evaluated according to the Japanese classification of gastric cancer and the Lauren classification. The clinicopathological data of the patients and tumors are summarized in Table I. Cylindrical tissue cores of 2 mm from the primary FFPE blocks were arrayed by using the manual device KIN-1 (Azumaya, Tokyo, Japan). Two representative cores were taken from each tissue block. The resulting tissue array blocks were then sectioned at 4 μ m in thickness and placed on slides. Cancers occupying more than half of the core area were evaluated by immunohistochemistry.

Immunohistochemical staining. Paraffin sections were dewaxed in xylene and rehydrated through graded ethanol to distilled water. Tissue arrays were stained with rabbit polyclonal antibodies against human CD73 (HPA017357, 1:5000, Atlas Antibodies, Stockholm, Sweden), human CD90 (HPA003733, 1:100, Atlas Antibodies, Stockholm, Sweden) and human CD105 (HPA011862, 1:500, Sigma-Aldrich, St. Louis, USA) using the EnVision FLEX system (Agilent, Santa Clara, USA). Antigen retrieval was performed via water bath heating for 40 min in retrieval buffers (pH9 for CD73 and CD105, pH6 for CD90). Positive staining was scored only in spindle cells. Since endothelial cells are also spindle-shaped, spindle cells forming a lumen structure were excluded from scoring (19). Scoring scale was as follows (Figure 1): for CD73, according to the positivity rate in a high power field; 0 [0-10%], 1 [10-50%], 2 [50-100%]. For CD90 and CD105, 0 [absent], 1 [positive in small aggregates], 2 [positive in diffuse fashion], 3 [highly positive area in more than half of core field]. Scoring was performed by two independent pathologists. In case of discordance, a consensus was reached through discussion. After scoring, gastric cancer cases were divided into negative- (score 0) and positive- (score $\geq$ 1) expression groups for CD73, CD90 and CD105. Epstein-Barr virus (EBV) infection was evaluated by EBER *in situ* hybridization as previously described (18).

Statistical analyses. Chi-square test was used to determine whether there was significant association between MSC marker expression and clinicopathological features. The *t*-test was used for comparisons between two samples from the same population after stratification. Survival curves were estimated by the Kaplan–Meier method and compared by the log-rank test. Multivariate analyses were performed using Cox proportional hazards model. For the latter, scoring data of miR-21 expression and EBER *in situ* hybridization from our previous report were used (18). All *p*-values of less than 0.05 were regarded as significant.

Results

Expression of MSC markers in spindle-shaped gastric cancer stroma cells. All markers showed membranous staining, while CD73 and CD90 were also found in the cytoplasm. The expression of CD73, CD90 and CD105 was detected in mononuclear cells and, in some cases, in vascular endothelial cells, and spindle-shaped cells; CD73 was also expressed in

Table I. Patients and gastric cancer cases characteristics.

Characteristic	n
Patients	524
Tumor cases	546
Age (years)	67.8 $\pm$ 10.9*
Gender (male/female)	373/151
Tumor size (mm)	55.1 $\pm$ 50.7*
Tumor stage (early/advanced) [†]	207/317
Lauren classification (intestinal/diffuse)	286/238
Lymphatic infiltration (negative/positive)	247/277
Venous infiltration (negative/positive)	250/274
Lymph node metastasis (negative/positive)	258/266
EBV (negative/positive)	485/39

*Mean $\pm$ standard deviation. [†]Early=Tis or T1, in TNM classification.

Table II. Distribution of immunostaining scores in spindle cells.

Score	CD73	CD90	CD105
0	356	213	485
1	93	192	59
2	97	122	2
3	-	19	0

Table III. Correlation between the expressions of the examined MSC markers.

	CD73			CD90		
	Negative	Positive	<i>p</i> -Value	Negative	Positive	<i>p</i> -Value
CD90						
Negative	188	25	<0.0001			
Positive	168	165				
CD105						
Negative	330	155	0.0002	208	277	<0.0001
Positive	26	35		5	56	

cancer cells. In gastric cancer stroma, 190 (34.8%) cases were positive for CD73, 333 (61.0%) cases for CD90 and 61 (11.2%) cases for CD105 (Table II). In addition, there was a positive correlation among the expression of CD73, CD90 and CD105 (*p*<0.0001 for CD73 and CD90, *p*=0.0002 for CD73 and CD105, and *p*<0.0001 for CD90 and CD105) (Table III).

MSC marker expression was related to disease progression. The association of each MSC marker with clinico-

Figure 1. Immunohistochemical assessment of the expression of each marker in spindle cells of gastric cancer stroma. Representative cases are shown; CD73 (A: score 0-2), CD90 (B: score 0-3), CD105 (C: score 0-2). Scale bar=100 μ m.

pathological features was examined (Table IV). The expression of all markers was positively correlated with larger tumor size ($p=0.0001$ for CD73, $p<0.0001$ for CD90, $p=0.0009$ for CD105), advanced cancer ($p<0.0001$ for CD73, CD90 and CD105), venous infiltration ($p<0.0001$ for CD73 and CD90, $p=0.001$ for CD105), lymphatic infiltration ($p<0.0001$ for CD73, CD90 and CD105) and lymph node

metastasis ($p<0.0001$ for CD73 and CD90, $p=0.0002$ for CD105). Concerning CD73 and CD90 markers, positivity was also associated with diffuse type in Lauren's classification ($p=0.009$ for CD73, $p=0.0002$ for CD90). These results suggest that the expression of the examined MSC markers in gastric cancer stroma is associated with disease progression.

Table IV. Clinicopathological features and MSC markers.

	CD73			CD90			CD105		
	Negative	Positive	p-Value	Negative	Positive	p-Value	Negative	Positive	p-Value
Gender									
Male	258	134	0.690	154	238	0.846	349	43	0.88
Female	98	56		59	95		136	18	
Age (years)	67.3±11.4 [†]	69.0±10.0	0.075	67.8±11.5	68.0±10.6	0.799	67.6±11.2	70.0±8.5	0.115
Size (mm)	47.8±54.6 [†]	65.3±38.4	0.0001	38.0±36.5	63.9±55.1	<0.0001	51.2±50.2	73.9±46.7	0.0009
Stage									
Early	200	27	<0.0001	153	74	<0.0001	220	7	<0.0001
Advanced	156	163		60	259		265	54	
Venous infiltration									
Negative	218	53	<0.0001	166	105	<0.0001	253	18	0.001
Positive	138	137		47	228		232	43	
Lymphatic infiltration									
Negative	213	53	<0.0001	157	109	<0.0001	252	14	<0.0001
Positive	143	137		56	224		233	47	
Lymph node metastasis									
Negative	228	49	<0.0001	163	114	<0.0001	260	17	0.0002
Positive	128	141		50	219		225	44	
Lauren's classification									
Diffuse	143	99	0.009	73	169	0.0002	210	32	0.218
Intestinal	213	91		140	164		275	29	
EBV status									
Negative	322	183	0.016	199	306	0.618	449	56	0.797
Positive	34	7		14	27		36	5	

[†]Mean±standard deviation.

MSC markers and prognosis. The expression of CD73, CD90 and CD105 was associated with poorer prognosis ($p<0.0001$ for CD73 and CD105, $p=0.0001$ for CD90) (Figure 2). A multivariate analysis was performed that included CD73-positive spindle cells, CD90-positive spindle cells, CD105-positive spindle cells, stage, venous infiltration, lymphatic infiltration, lymph node metastasis, and miR-21 expression in cancer stroma (previous data (18)) and EBV status (previous data (18)). CD105-positive spindle cells were strongly associated with poor prognosis (Adjusted risk ratio=2.407, 95% CI=1.463-3.961, $p=0.0005$) (Table V).

Discussion

Previous studies indicated that the interaction between cancer cells and MSCs is involved in the epithelial to mesenchymal transition and in the differentiation of MSCs to CAFs, as well (6, 17). Hence, this interaction is a critical event in gastric cancer progression. To investigate the possible association of MSC features with gastric cancer progression, the correlation between the expression of three MSC markers, CD73, CD90 and CD105, in spindle-shaped stromal cells, and clinicopathological features was examined in a large number of cases. We found that the expression of these markers was

associated with larger tumor size, advanced stage, venous infiltration, lymphatic infiltration and lymph node metastasis. These data suggested the expression of MSC markers was associated with disease progression.

There are several reports regarding the relationship between the tested MSC markers and cancer. Contrary to our results, CD73 expression in cancer stroma was associated with better prognosis in rectal cancer (20) and prostate cancer (21). This could be attributed to the possibility that the stromal component included round immune cells in these reports. However, this discrepancy needs to be further explored. CD90 can be expressed in the cancer stroma of prostate (22), lung (23) and gastric cancer (24). In lung cancer, it was that suggested CD90 is a CAF marker (23). CD90-positive CAFs affect the prostate cancer stem cell niche (22) and promote lung cancer cell proliferation and dissemination (25). Moreover, *in vivo* studies in mice and *in vitro* experiments in human prostate-derived CAFs have demonstrated that CD105 expression was also involved in prostate cancer progression (26). Authors suggested that CD105-positive fibroblasts were derived from myofibroblasts rather than from resident fibroblasts (26).

A recent report, based on human clinical samples, showed that high percentage of triple-positive (CD73⁺/CD90⁺/CD105⁺) stromal cells from high-grade glioma tissue

Figure 2. Overall survival and MSC marker expression. In the examined gastric cancer cases, cells expressing the marker CD73 (A), CD90 (B), or CD105 (C) (Positive group) were significantly associated with poorer overall survival ($p < 0.0001$, $p = 0.0001$, and $p < 0.0001$, respectively), compared to the cells that did not express these markers (Negative group).

Table V. Prognostic factors for patient survival in univariate and multivariate analyses.

Characteristics	Unadjusted risk ratio (95% CI)	p-Value	Adjusted risk ratio (95% CI)	p-Value
CD73 ⁺ spindle cells	2.251 (1.554-3.262)	<0.0001	0.908 (0.597-1.383)	0.6540
CD90 ⁺ spindle cells	2.202 (1.461-3.320)	0.0002	0.669 (0.403-1.111)	0.1205
CD105 ⁺ spindle cells	3.153 (1.986-5.004)	<0.0001	2.407 (1.463-3.961)	0.0005
miR-21 expression	1.747 (1.214-2.515)	0.0027	1.020 (0.694-1.499)	0.9195
Advanced stage	7.013 (4.211-11.68)	<0.0001	3.745 (1.814-7.735)	0.0004
Lymphatic infiltration	3.790 (2.522-5.694)	<0.0001	1.173 (0.690-1.994)	0.5559
Venous infiltration	3.657 (2.450-5.457)	<0.0001	1.270 (0.772-2.089)	0.3471
Lymph node metastasis	4.508 (2.979-6.821)	<0.0001	2.208 (1.266-3.853)	0.0053
Positive EBV status	0.399 (0.175-0.908)	0.0285	0.434 (0.190-0.994)	0.0484

CI, Confidence interval; EBV, Epstein-Barr virus.

(Glioma-associated MSCs) were correlated with poor prognosis (27). Herein, co-expression of CD73, CD90, and CD105 was not examined, but a positive correlation among them was revealed. According to multivariate analysis, among the three MSC markers, CD105 was the most important prognostic factor of overall survival of gastric cancer. This predominance of CD105 over other MSC markers was also suggested in multipotency, one of the essential traits of MSCs, where CD73⁺/CD105⁺ dermal fibroblasts showed differentiation into both adipocytes and osteocytes, whereas CD73⁺/CD105⁻ dermal fibroblasts did not (28). This difference among markers could be partly explained from the close relationship between CD105 and TGF-beta signaling. CD105 is a co-receptor of TGF-beta, which directly modulates signaling (29). This process is necessary for angiogenesis and vasculogenesis in endothelial cells or immature mesenchymal cells, as well as for fibrosis in fibroblasts in benign and malignant states (30). In the human stomach, TGF-beta 1 was expressed in epithelial cells and cancer cells closely associated with CD105-positive neo-vessels (31). High density of CD105-positive micro-vessels (neo-vessels) was associated with poorer prognosis in several types of cancer (29).

Since endothelial cells are spindle-shaped (3), we defined "spindle cells" as cells with a spindle-shaped morphology without lumen formation (19). However, there is a possibility that "spindle cells" included the endothelium of collapsed or immature vessels with obscured lumens. On the other hand, it is also possible that aggregates of CD105-positive spindle cells were immature mesenchymal cells associated with vasculogenesis.

Our study showed that CD105-positive spindle stromal cells are strongly associated with disease progression and poor prognosis of gastric cancer, suggesting that these cells may represent a promising therapeutic target for gastric cancer.

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