Circulating galectin-3 correlates with angiogenetic factors and indicators of systemic inflammation in patients with stage IV esophageal cancer

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Abstract

Background and Aims: The significance of circulating galectin-3 in esophageal cancer has not yet been elucidated. The aim of this study was to identify the relationships between circulating galectin-3 and angiogenetic, nutritional, and inflammatory factors in patients with stage IV esophageal cancer.

Materials and Methods: We investigated the relationships between the level of circulating galectin-3 and angiogenetic factors, such as interleukin (IL)-6, vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), and soluble intercellular adhesion molecule-1 (sICAM-1), and nutritional and inflammatory indicators in 11 patients with stage IV esophageal cancer.

Results: The concentration of galectin-3 in patients with stage IV esophageal cancer was significantly higher than in healthy volunteers. The amount of circulating galectin-3 correlated with the amount of serum IL-6 (r = 0.636, P < 0.05), VEGF (r = 0.721, P < 0.05), sICAM-1 (r = 0.745, P < 0.01), and C-reactive protein (r = 0.786, P < 0.05), as well as the lymphocyte count (r = −0.718, P < 0.05), and the neutrophil / lymphocyte ratio (r = 0.718, P < 0.05).

Conclusions: Galectin-3 may play a key role in progression of tumors by increasing the production of angiogenetic factors, leading to malnutrition by persistent systemic inflammation.

Key Words: galectin-3, esophageal cancer, vascular endothelial growth factor (VEGF), interleukin (IL)-6, soluble intercellular adhesion molecule-1 (sICAM-1)

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The aim of this study was to identify the relationships between circulating galectin-3 and angiogenetic, nutritional, and inflammatory factors in patients with stage IV esophageal cancer.

Materials and Methods

Patients. Blood samples were collected from 11 patients with stage IV esophageal cancer between June 2011 and December 2012 before the patients had undergone any treatment. All patients were confirmed histologically that they had a squamous cell carcinoma of the esophagus. We used The Japanese Classification of Esophageal Cancer (12th edition) when determining the stage of disease in each patient. The mean age was 67.3 ± 8.2 years, and all patients were male. Sera from the patients were stored at −80°C until use, and each sample was used only once after thawing. In addition, samples from 20 healthy volunteers of similar age and gender distributions to the patients were used as controls. The study protocol was approved by the Ethics Committee of Fukushima Medical University, and written informed consent was obtained from the enrolled patients and healthy volunteers.

Measurement of Galectin-3, angiogenetic factors. Serum concentrations of galectin-3, IL-6, vascular endothelial growth factor (VEGF), G-CSF, and sICAM-1 were measured using an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) according to the manufacturer’s instructions.

Parameters for nutritional status and inflammation. The nutritional status of each patient was determined by measuring serum concentrations of RBP (by latex agglutination immunoassay), prealbumin (by turbidimetric immunoassay) and transferrin (by turbidimetric immunoassay). C-reactive protein (CRP), neutrophil and lymphocyte counts, and neutrophil / lymphocyte ratio (NLR) were used as indicators of inflammation.

Statistical analysis. Differences between the groups were analyzed using the Student’s t-test, and associations between two variables were quantified using the Spearman’s rank correlation coefficient. A P value of < 0.05 was considered statistically significant. All statistical calculations were performed using SPSS® version 22 (IBM Japan, Tokyo, Japan). Not all blood samples were of sufficient volume for all measurements.

Results

As shown in Fig. 1, the concentration of galectin-3 in patients with stage IV esophageal cancer was significantly higher than in healthy volunteers (esophageal cancer vs. healthy volunteers: 10.9 ± 4.5 vs. 3.1 ± 1.4 ng/ml [mean ± SD], P < 0.001).

Fig. 2 shows the relationship between the serum levels of galectin-3 and angiogenetic factors. There were statistically significant correlations between the circulating amount of galectin-3 and IL6 (r = 0.636, P < 0.05), VEGF (r = 0.721, P < 0.05), and sICAM-1 (r = 0.745, P < 0.05). However, the concentration of serum galectin-3 exhibited no significant correlation with G-CSF (r = 0.236, P = 0.48).

Fig. 3 shows the relationship between the serum levels of galectin-3 and nutritional condition parameters. The concentration of serum galectin-3 showed weak correlations with RBP (r = 0.523, P = 0.09), prealbumin (r = −0.582, P = 0.06), and transferrin (r = −0.588, P = 0.07). However, no statistically significant differences were observed.

Fig. 4 shows the relationship between the concentrations of galectin-3 and indicators of inflammation. The amount of circulating galectin-3 exhibited strong correlations with CRP (r = 0.786, P < 0.05), lymphocyte count (r = −0.718, P < 0.05), and NLR (r = 0.718, P < 0.05). No statistically significant correlation was observed between the amount of serum galectin-3 and neutrophil count (r = 0.571, P = 0.07).

Discussion

This study reports for the first time the amount of galectin-3 in patients with stage IV esophageal cancer. Angiogenesis is a critical step in the formation of metastatic foci. Thus, we investigated the relationship between circulating galectin-3 and stage IV esophageal cancer. Circulating galectin-3 concentration correlated with IL-6, VEGF, and sICAM-1, which are strong pro-angiogenesis factors. Among the patients enrolled in the present study, eight patients had metastasis to other organs or distant lymph node metastases, and seven patients had tumors invading adjacent organs (T4b). Galectin-3 was reported to regulate the production of IL-6, G-CSF, granulocyte macrophage colony-stimulating factor, and sICAM-1 in vitro. Thus, circulating galectin-3 plays a key role in angiogenesis. In an in vitro study, galectin-3 was used at a high concentration of 25 μg/ml or more, although the concentration of circulating galectin-3 was usually < 1 μg/ml. However, there is evidence that galectin-3 receptors could enhance the galectin-3 binding affinity by as much as 10,000-fold[17,18].

The assessment of nutritional status is essential for a diagnosis of nutritional compromise, and measurements of serum concentrations of RTPs such as RBP, prealbumin, and TF have been reported to be more accurate for assessment than albumin[19,20]. Galectin-3 may play a role in the development of malnutrition, although galectin-3
Fig. 1 The concentration of galectin-3 in patients with stage IV esophageal cancer. The concentration of galectin-3 in patients with stage IV esophageal cancer showed a statistically significant elevation than those of healthy volunteers (esophageal cancer vs. healthy volunteers: $10.9 \pm 4.5$ vs. $3.1 \pm 1.4$ ng/ml [mean ± SD], $P < 0.001$).

Fig. 2 Correlation of circulating galectin-3 with angiogenic factors. There were statistically significant correlations between the circulating amount of galectin-3 and IL6 ($r = 0.636$, $P < 0.05$), vascular endothelial growth factor (*VEGF) ($r = 0.721$, $P < 0.05$), and soluble form of intercellular adhesion molecule (**sICAM-1) ($r = 0.745$, $P < 0.01$).

Fig. 3 Correlation of galectin-3 with parameters of nutritional condition. The concentration of serum galectin-3 showed weak correlations with retinol binding protein ($r = 0.523$, $P = 0.09$), prealbumin ($r = -0.582$, $P = 0.06$), and transferrin ($r = -0.588$, $P = 0.07$). However, no statistically significant differences were observed.
concentration showed weak correlations with these nutritional condition indicators.

Galectin-3 exhibited strong correlations with angiogenic factors, such as VEGF, IL-6, and sICAM-1. VEGF, previously known as vascular permeability factor, has a molecular weight of 45 kDa and belongs to a family of platelet-derived growth factors. Several isoforms have been identified, including isoforms A, B, C, D, and E. VEGF has been reported to play a role not only in the progression of malignant tumors but also in immunomodulation. Elevated VEGF levels are reportedly associated with advanced-stage melanoma, along with negative immune reactions, including type 2 helper T cell and impaired dendritic cell function. IL-6 is a pleiotropic cytokine that plays diverse roles as a regulator of immunological responses. Galectin-3 plays a role in the regulation of IL-6 production and inhibition of natural killer (NK) cell-mediated toxicity.

In the present study, galectin-3 had a strong correlation with NLR. NLR has been reported to be a marker of systemic inflammatory responses and to increase risk of tumor progression. Persistent systemic inflammation can be a predisposing factor to malnutrition, resulting in cancer cachexia.

Taken together, galectin-3 may play a role as a key factor in tumor progression by increasing the production of angiogenic factors, leading to malnutrition by persistent systemic inflammation.

References
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