# Association between circulating galectin-3 levels and the immunological, inflammatory and nutritional parameters in patients with colorectal cancer

TATSUO SHIMURA<sup>1</sup>, MASAHIKO SHIBATA<sup>2</sup>, KENJI GONDA<sup>2</sup>, TAKAHIRO NAKAJIMA<sup>3</sup>, SHUN CHIDA<sup>3</sup>, MASARU NODA<sup>3</sup>, SATOSHI SUZUKI<sup>3</sup>, IZUMI NAKAMURA<sup>3</sup>, SHINJI OHKI<sup>3</sup> and SEIICHI TAKENOSHITA<sup>3</sup>

<sup>1</sup>Department of Cancer Biology and Electronics, Fukushima Medical University, Fukushima 960-1295;

<sup>2</sup>Department of Gastrointestinal Oncology, Saitama Medical University International

Medical Center, Hidaka, Saitama 350-1298; <sup>3</sup>Department of Organ Regulatory

Surgery, Fukushima Medical University, Fukushima 960-1295, Japan

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**Abstract.** Galectin-3, a  $\beta$ -galactoside-binding lectin, exhibits pleiotropic biological functions and has a role as one of the immunological modulators. However, the associations between circulating galectin-3 and immunological, inflammatory and nutritional parameters have not yet been fully elucidated. The serum concentration of galectin-3 was examined in association with interleukin-10 (IL-10), IL-12 and IL17 production, lymphocyte stimulation, neutrophil/lymphocyte ratio (NLR), white blood cell count (WBC), C-reactive protein (CRP) and rapid turnover proteins, including retinol-binding protein (RBP), prealbumin (PA) and transferrin (TF) in 50 patients with untreated colorectal cancers. Significant increases (P<0.05) were observed in the serum galectin-3 levels in patients with untreated colorectal cancer (9.6±4.5 ng/ml) compared with the normal controls  $(3.2\pm1.6 \text{ ng/ml})$ . Higher serum galectin-3 concentrations were observed in patients with colon cancer (11.5±4.4 ng/ml) compared to in patients with rectal cancer (8.0±4.0 ng/ml) (P=0.005). The levels of circulating galectin-3 inversely correlated with the production of IL-10 (r=-0.59, P<0.001), and IL-12 (r=-0.69, P<0.001). Galectin-3 concentration also inversely correlated with the lymphocyte stimulation assay stimulation index (r=-0.42, P=0.021). However, the level of serum galectin-3 correlated with IL-17 production (r=0.67, P<0.001). Serum galectin-3 levels exhibited significant correlations with NLR (r=0.41, P=0.009), WBC (r=0.32, P=0.035), and CRP (r=0.63, P<0.001), and statistically significant inverse correlations with RBP (r=-0.45, P=0.002), PA (r=-0.46, P=0.001) and TF (r=-0.72, P<0.001). Galectin-3 may be one of the key factors in the regulation of immunological, inflammatory and nutritional conditions.

## Introduction

Galectin-3, a  $\beta$ -galactoside-binding lectin, exhibits pleiotropic biological functions and has been implicated in cell growth, differentiation, apoptosis, adhesion, malignant transformation and RNA processing (1-4). Galectin-3 is expressed intracellularly and extracellularly by numerous cell types.

Cytoplasmic galectin-3 acts as an apoptosis inhibitor in the cytoplasm and, in certain conditions, regulates trafficking between the cytoplasm and the nucleus (3). Nuclear galectin-3 has been reported to function as an mRNA splicing promoter (5). When expressed on the surface of tumor cells, galectin-3 has a role as an adhesion molecule in cell-to-cell or cell-to-matrix interactions (6). Circulating galectin-3 has been reported to be produced by activated macrophages, mast cells, eosinophils and tumor cells (7).

Galectin-3 also has a role as an immunological modulator by regulating cytokine production, phagocytosis, chemotaxis and apoptosis induction (8-12). As for cytokine production, galectin-3 has been reported to have inhibitory effects on interleukin-12 (IL-12) production by dendritic cells (9). Macrophages from galectin-3 deficient mice produce higher amounts of IL-10 compared with those from wild-type mice (11). The production of IL-6 has been reported to be influenced by galectin-3 through the tumor-producing galectin-3 binding protein (13). As for cellular immunity, galectin-3 has been shown to reduce the affinity of T-cell receptors (14), influence the strength of antigen activation

*Correspondence to:* Professor Tatsuo Shimura, Department of Cancer Biology and Electronics, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan E-mail: tshimura@fmu.ac.jp

*Abbreviations:* IL, interleukin; PBMCs, peripheral blood mononuclear cells; NLR, neutrophil/lymphocyte ratio; WBC, white blood cell count; CRP, C-reactive protein; RBP, retinol-binding protein; PA, prealbumin; TF, transferrin; ELISA, enzyme-linked immunosorbent assay

*Key words:* galectin-3, IL-10, IL-12, IL-17, rapid turnover protein, retinol binding protein, prealbumin, transferrin

Α

12

10

in dendritic cells (15,16), internalize T-cell receptors (17) and induce apoptosis of T cells (12). Galectin-3 also inhibits natural killer (NK) cell-mediated tumor immunity by binding the natural cytotoxicity receptor, NKp30 or NKG2D (18,19).

Previous studies have revealed an elevated concentration of serum galectin-3 in various cancers, including breast (20), colorectal (21,22), stomach (23), lung (20), bladder (24), head and neck (25), liver (26), thyroid (27), pancreatic (28) and melanoma (29). These studies demonstrated higher amounts of galectin-3 in the sera of patients and its association with poorer prognosis. However, the associations between galectin-3 and immunological and nutritional parameters remain to be elucidated.

The aim of the present study was to clarify the associations between circulating galectin-3 and host immunity and nutritional status. IL-10, IL-12 and IL17 production were examined by peripheral blood mononuclear cells (PBMCs) and lymphocyte stimulation assay as immunological parameters, neutrophil/lymphocyte ratio (NLR), white blood cell count (WBC) and C-reactive protein (CRP) as markers of inflammation, and rapid turnover proteins (RTP), such as retinol-binding protein (RBP), prealbumin (PA) and transferrin (TF) as parameters for nutritional condition.

## Materials and methods

Patients. Blood samples were collected from 50 patients with colorectal cancer before starting treatment between April 2011 and August 2013. The patients included 8 with stage I disease, 12 with stage II disease, 18 with stage III disease, and 12 with stage IV disease. The enrolled patients underwent surgery or chemotherapy for the treatment of histologically confirmed cancer at the Department of Organ Regulatory Surgery, Fukushima Medical University (Fukushima, Japan). In addition, samples from 20 healthy volunteers of similar age and gender distributions 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.

Blood samples. PBMCs were separated on Ficoll-Hypaque (Pharmacia-Biotech, Uppsala, Sweden) columns. The isolated PBMCs were washed twice with RPMI-1640 (Wako Pure Chemical Industries Ltd., Osaka, Japan). Sera from patients were stored at -80°C until use.

Galectin-3 measurement. Serum concentrations of galectin-3 were measured using an enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA) according to the manufacturer's protocol.

Cytokine production by PBMCs. PBMCs, prepared using the aforementioned method, were incubated in 1 ml of RPMI-1640 at a concentration of 10<sup>6</sup> cells/ml with 10% heat-inactivated fetal calf serum (Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA) in 5% CO<sub>2</sub> at 37°C for 24 h with appropriate stimulations: With 20  $\mu$ g/ml phytohemagglutinin (PHA) for IL-10 and IL-17 production assays, and with 0.01% of Staphylococcus aureus Cowan-1 for the IL-12 production assays. Aliquots of these supernatants were frozen and stored



В 18

P < 0.001

16

14

P = 0.005

cancer. (A) Significant increases (P<0.05) were observed in serum galectin-3 levels in patients with untreated colorectal cancer compared with normal controls. (B) When serum galectin-3 concentrations were compared between patients with colon cancer (n=23) and patients with rectal cancer (n=27), the levels of serum galectin-3 in patients with colon cancer were significantly higher than those in patients with rectal cancer (P=0.005). (C) No statistically significant differences were observed in the levels of serum galectin-3 between the different stages.

at -80°C until use. Supernatant samples were subsequently thawed and used for measurements of IL-10, IL-12 and IL-17 concentrations using ELISA (R&D Systems). Each sample was used only once subsequent to thawing.

Lymphocyte stimulation assay. A lymphocyte proliferation assay was performed using prepared PBMCs suspended in RPMI-1640 containing 10% fetal calf serum. After the addition of 10 µg/ml PHA into PBMC culture wells stored at 37°C in a 5% CO<sub>2</sub> atmosphere, mitogenesis was observed for 80 h. <sup>3</sup>H-thymidine (Japan Radioisotope Association, Tokyo, Japan) was added to wells for the last 8 h of incubation. Cells were harvested and 3H-thymidine incorporation was determined using a liquid scintillation counter (Perkin-Elmer, Waltham, MA, USA) and expressed as counts per minute (cpm). The stimulation index (SI) was obtained by calculating total cpm/control cpm. The controls were PBMCs without PHA addition.

Parameters for nutritional status and inflammation. The patient nutritional statuses were determined by measuring serum concentrations of RBP (latex agglutination immunoassay), PA (turbidimetric immunoassay) (30) and TF (turbidimetric immunoassay) (31). Neutrophil and lymphocyte counts, as well as NLR, were used as indicators of inflammation.

*Statistical analysis.* Differences between the groups were analyzed using the Student's t-test. Associations between two variables were quantified using the Spearman's rank correlation coefficient. P<0.05 was considered to indicate a statistically significant difference. All the statistical calculations were performed using SPSS<sup>®</sup> version 22 (IBM Corp. Japan, Tokyo, Japan). Not all blood samples were of sufficient volume for all measurements.

#### Results

Serum galectin-3 levels in patients with untreated colorectal cancer. As shown in Fig. 1A, significant increases (P<0.05) were observed in serum galectin-3 levels in patients with untreated colorectal cancer (9.6 $\pm$ 4.5 ng/ml) compared with normal controls (3.2 $\pm$ 1.6 ng/ml). When serum galectin-3 concentrations were compared between patients with colon cancer (n=23) and patients with rectal cancer (n=27), the levels of serum galectin-3 in patients with colon cancer (11.5 $\pm$ 4.4 ng/ml) were significantly higher than those in patients with rectal cancer (8.0 $\pm$ 4.0 ng/ml) (Fig. 1B, P=0.005). However, no statistically significant differences were observed in the levels of serum galectin-3 between the different stages (9.8 $\pm$ 4.6, 8.1 $\pm$ 5.1, 9.6 $\pm$ 4.6 and 11.1 $\pm$ 2.8 ng/ml for stages 1-4, respectively; Fig. 1C).

Correlation between the galectin-3 serum concentrations and the immunological parameters. Fig. 2 shows the results of the correlation analysis between the galectin-3 serum concentrations and the immunological parameters. The amount of circulating galectin-3 inversely correlated with the production of IL-10 (r=-0.59, P<0.001) and IL-12 (r=-0.69, P<0.001). The serum concentration of galectin-3 also inversely correlated with the SI (r=-0.42, P=0.021). By contrast, the level of serum galectin-3 correlated with the production of IL-17 (r=0.67, P<0.001).

Correlation analysis between the galectin-3 serum concentrations and inflammation indicators. Fig. 3 shows the results of the correlation analysis between the galectin-3 serum concentrations and inflammation indicators. The levels of serum galectin-3 exhibited significant correlations with NLR (r=0.41, P=0.009), WBC (r=0.32, P=0.035) and CRP (r=0.63, P<0.001).

*Correlation analyses in association with the nutritional parameters.* The results of the correlation analyses in association with the nutritional parameters are summarized in Fig. 4. The level of serum galectin-3 exhibited statistically significant inverse correlations with RBP (r=-0.45, P=0.002), PA (r=-0.46, P=0.001) and TF (r=-0.72, P<0.001).

## Discussion

In accordance with the previous studies, the serum concentration of galectin-3 in the cancer patients was significantly higher compared to the healthy volunteers. However, no statistically significant differences were observed when comparing disease stages. Immunohistochemicaly, strong expression of galectin-3 has been reported to be associated with disease progression and metastasis (32,33). The sources of circulating galectin-3



Figure 2. Correlations between the galectin-3 serum concentrations and immunological parameters. The amount of circulating galectin-3 inversely correlated with the production of (A) IL-10 (r=-0.59, P<0.001) and (B) IL-12 (r=-0.69, P<0.001). The serum concentration of galectin-3 also inversely correlated with the (D) stimulation index (r=-0.42, P=0.021). By contrast, the level of serum galectin-3 correlated with the production of (C) IL-17 (r=0.67, P<0.001). IL, interleukin.

are not only tumor cells, but also macrophages, mast cells and eosinophils (7,20). Thus, the circulating level of galectin-3 is not always representative of the expression level of galectin-3 in the tumor microenvironment. The reason for why the levels of serum galectin-3 in patients with colon cancer were significantly higher compared to those in patients with rectal cancer remains to be elucidated.

The amount of circulating galectin-3 showed a significant correlation with IL-17 production, whereas an inverse correlation was observed with IL-12 production. To the best of our knowledge, the present study reports for the first time the association between galectin-3 and IL-17 production, while



Figure 3. Correlations between the galectin-3 serum concentrations and inflammation indicators. The levels of serum galectin-3 exhibited significant correlations with (A) neutrophil/lymphocyte ratio (r=0.41, P=0.009), (B) white blood cell count (r=0.32, P=0.035) and (C) CRP (r=0.63, P<0.001). CRP, C-reactive protein.

galectin-3 has been reported to have inhibitory effects on IL-12 production by dendritic cells (9). Our previous study reported that increased IL-17 production correlated with cellular immunosuppression (34). Thus, cell-mediated immunity may be depressed through Th2-dominant conditions driven by depressed IL-12 production. By contrast, the production of IL-10, which is a potent immunosuppressive cytokine produced primarily by Th2 cells, macrophages and activated B cells, showed inverse correlation with the amount of circulating galectin-3. The direct effects of galectin-3 on IL-10, IL-12 and IL-17 production should be assessed in the future.

As for indicators of inflammation, NLR, WBC and CRP exhibited significant correlations with the level of serum galectin-3. The present study supports a previous study that galectin-3 is associated with systemic inflammation and fibrosis (7). Systemic chronic inflammation has been reported to have a role in tumor development and growth, and importantly in the suppression of tumor immunity (35,36).

The assessment of nutritional status is essential for a diagnosis of nutritional compromise, and measurements of serum concentrations of RTPs such as RBP, PA and TF have been



Figure 4. Correlations between serum galectin-3 concentration and nutritional parameters. The level of serum galectin-3 exhibited statistically significant inverse correlations with (A) retinol-binding protein (r=-0.45, P=0.002), (B) prealbumin (r=-0.46, P=0.001) and (C) transferrin (r=-0.72, P<0.001).

reported to be more accurate for this assessment in comparison to albumin (37-39). The serum concentration of galectin-3 showed a significant inverse correlation with assessed RTPs. The key mechanisms leading to cancer cachexia in which nutritional impairment is a major clinical issue, are mostly immune reactions caused by chronic inflammation. Galectin-3 may be one of the key factors in the regulation of immunological, inflammatory and nutritional conditions.

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