Intracellular accumulation of galectin-3 is associated with a poor prognosis in patients with invasive intraductal papillary mucinous neoplasms

Tatsuo Shimura1), Yasuhide Kofunato2), Ryo Okada2), Rei Yashima2), Yoshihisa Koyama2), Koji Okada3), Kenichiro Araki3), Yasuo Hosouchi3), Hiroyuki Kuwano3), Seiichi Takenoshita3)

1) Department of Cancer Biology and Electronics, Fukushima Medical University
2) Department of Organ Regulatory Surgery, Fukushima Medical University
3) Department of General Surgical Science, Gunma University Graduate School of Medicine
4) Department of Surgery and Laparoscopic Surgery, Gunma Prefecture Saiseikai-Maebashi Hospital

Abstract

Background: Although intraductal papillary mucinous neoplasms (IPMNs) have become recognized as the most common cystic tumors of the pancreas, evaluations of the prognostic factors of invasive IPMN have not yet been firmly established. Furthermore, the significance of galectin-3 expression in the prognosis of IPMN has not yet been examined.

Materials and Methods: We retrospectively examined galectin-3 expression immunohistochemically in 53 patients with IPMNs who underwent resection: 28 patients with non-invasive IPMN (including 3 patients with IPMN with carcinoma in situ component), and 25 patients with invasive IPMN.

Results: The intracellular accumulation of galectin-3 (gal-3-INA) was more frequently encountered in patients with invasive IPMN than with non-invasive IPMN (P = 0.038). Incidences of background fibrosis and dilatation of the main pancreatic duct were higher in the high-galectin-3 expression group than in the low-galectin-3 expression group (P = 0.004 and 0.008, respectively). Incidence of background fibrosis was also higher in patients with gal-3-INA than without gal-3-INA (P = 0.011). The presence of gal-3-INA was higher in the high-galectin-3 expression group than in the low-galectin-3 expression group (P = 0.014). The high-galectin-3 expression group and the patients with gal-3-INA had a significantly poorer prognosis than the low-galectin-3 expression group and those without gal-3-INA (P = 0.020 and P = 0.014, respectively). Multivariate analysis using a Cox regression model revealed that gal-3-INA was an independent prognostic factor (hazard ratio: 5.162, 95% confidential interval: 1.033-25.807, P = 0.046).

Conclusions: The presence of gal-3-INA is an independent prognostic factor for patients with invasive IPMN.

Key Words: galectin-3 intraductal papillary mucinous neoplasm (IPMN), prognosis

Introduction

Intraductal papillary mucinous neoplasms (IPMNs) have become recognized as the most common cystic tumors of the pancreas, accounting for up to 70% of all cases1). On the basis of the location of ductal involvement, IPMNs are divided into three groups: main duct IPMN, branch duct IPMN, and mixed type IPMN2). For the management of IPMN, the first International Consensus Guidelines were published in 20063), and they were updated in 20124). According to the Guidelines, surgical resection is recommended for all main duct IPMNs because of the high risk of malignancy (61.6%) and invasive carcinoma (43.1%)5, 6).

Long-term survival for completely resected IPMNs is markedly better than that of invasive ductal carcinoma of the pancreas5-10), whereas some reported invasive IPMNs behave as aggressively as invasive ductal carcinoma11). The recurrence rate of invasive IPMNs after complete resection ranges from 40 to 65% of patients, and lymph node involvement, vascular invasion, positive surgical margin, and existence of jaundice are prognostic factors12, 13). However, evaluations for such prognostic factors have not yet been firmly established.

On the other hand, the lack of a clear definition of malignancy of IPMN makes it difficult to compare described data. Some studies defined cases with carcinoma in situ as malignant IPMNs, while others defined only invasive IPMN as malignant IPMNs. The new International Consensus Guidelines described carcinoma in situ as high-grade dysplasia to avoid further confusion12).

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 processing14-17).
Overexpression of galectin-3 has been reported as a predictor of poorer prognosis in ovarian carcinoma\textsuperscript{18}, nasopharyngeal carcinoma\textsuperscript{19}, malignant melanoma\textsuperscript{20}, gallbladder carcinoma\textsuperscript{21}, osteosarcoma\textsuperscript{22}, and hepatocellular carcinoma\textsuperscript{23}. However, in pancreatic carcinoma\textsuperscript{24}, laryngeal squamous-cell carcinoma\textsuperscript{25}, gastric carcinoma\textsuperscript{26}, clear cell renal carcinoma\textsuperscript{27}, and breast carcinoma\textsuperscript{28}, said overexpression has been reported to be associated with better prognosis. As for the relationship between galectin-3 and IPMN, there is one report describing that the gene expression of galectin-3 was about 4.88-fold up-regulated in IPMN\textsuperscript{29}.

The aim of our study is to clarify the significance of the expression of galectin-3 in comparison between non-invasive and invasive IPMN, and the relationship between prognosis and galectin-3 expression in invasive IPMN.

**Materials and Methods**

**Patients**

We enrolled 53 patients with IPMNs who underwent resection of tumors between 2000 and 2010; 28 patients with non-invasive IPMN (including 3 patients with IPMN with carcinoma in situ component), and 25 patients with invasive IPMN. Minimally invasive IPMNs were defined as invasive IPMNs. The patients’ demographics are summarized in Table 1. Neoplasms in the head, neck or uncinate process of the pancreas were treated with pancreaticoduodenectomy, and those in the pancreatic body or tail were treated with open or laparoscopic distal pancreatectomy as appropriate. All patients gave written informed consent.

We examined the following clinical and pathologic features: age, gender, tumor size (< 3 cm vs. ≥ 3 cm), types of involved duct (main duct or mixed type vs. branch duct), with vs. without symptoms, cytology of pancreatic juice (≤ class III vs. ≥ class IV), tumor markers (with vs. without abnormality of carcinoembryonic antigen or carbohydrate antigen\textsuperscript{19-9}), single vs. multifocal lesion, with vs. without dilatation of the main pancreatic duct, with vs. without mural nodule in preoperative imaging examination, with vs. without background fibrosis, T factor (T1 or 2 vs. T3 or T4), with vs. without lymph node involvement, stage according to the Union for International Cancer Control classification (stage I vs. stage II or III), with vs. without microscopic lymphatic invasion, with vs. without microscopic vascular invasion, and with vs. without microscopic neural invasion.

**Immunohistochemical analysis**

Galectin-3 expression was assessed by immunohistochemistry using an avidin-biotin-peroxidase complex method. Formalin-fixed, paraffin-embedded tissue samples were cut into 4-μm-thick sections. The sections were deparaffinized in xylene and rehydrated through a
Expression of galectin-3 in IPMN

Expression of galectin-3

Fig. 1 shows galectin-3 expression in patients with invasive IPMN. In the specimens with gal-3-INA (Fig. 1B), galectin-3 existed predominantly in the nucleus; however, in those without gal-3-INA, galectin-3 existed mainly in the cytosol (Fig. 1A). Normal ductal epithelia and acinar cells appeared to be negative for galectin-3 expression, while neural tissues in the pancreas were strongly positive.

Patients' demographics

The average expression level of galectin-3 in all 53 patients was 44.0 ± 30.0% (mean ± SD), so we decided to classify the patients into two groups under the subheadings: the low-galectin-3 expression group; with an expression level of galectin-3 < 45.0%, and the high-galectin-3 expression group with an expression level of galectin-3 ≥ 45.0%.

The demographics of the patients with non-invasive or invasive IPMN are summarized in Table1. The incidence of having a mural nodule was higher in invasive IPMN than in non-invasive IPMN (P = 0.011). Gal-3-INA was more frequently encountered in patients with invasive IPMN than with non-invasive IPMN (P = 0.038). As for age, gender, type of involved duct, lesion size, with or without symptom, with or without ductal dilation and expression level of galectin-3, there was no statistically significant difference between non-invasive and invasive IPMN.

Table 2 shows the demographics of the patients with IPMN according to the galectin-3 expression level and the presence of gal-3-INA. Incidences of background fibrosis and dilatation of the main pancreatic duct were higher in the high-galectin-3 expression group than in the low-galectin-3 expression group (P = 0.0041 and P = 0.006, respectively). An incidence of background fibrosis...
was also higher in patients with gal-3-INA than without it ($P = 0.011$). Existence of gal-3-INA was higher in the high-galectin-3 expression group than in the low group ($P = 0.014$).

**Overall survival**

Table 3 shows the analysis of the pathological background of patients with invasive IPMN according to the expression level of galectin-3 and the presence of gal-3-INA. There was no statistically significant difference between the groups in each analysis. The median survival time of patients with invasive IPMN was 3.53 years. Fig. 2A shows the overall survival of patients according to the level of galectin-3 expression. There was a statistically significant difference between the groups ($P = 0.020$). Fig. 2B shows the overall survival of patients with or without gal-3-INA. The patients with gal-3-INA had a significantly poorer prognosis than those without gal-3-INA ($P = 0.014$).

The results of the univariate and multivariate analyses are shown in Table 4. Univariate analysis revealed that gal-3-INA (hazard ratio [HR]: 4.110, 95% confidential interval [CI]: 1.214-13.907, $P = 0.023$), T category (HR: 3.847, 95% CI: 1.151-12.861, $P = 0.029$), microscopic lymphatic invasion (HR: 11.572, 95% CI: 1.458-90.174, $P = 0.019$), microscopic vascular invasion (HR: 6.166, 95% CI: 1.795-21.173, $P = 0.004$), microscopic neural invasion (HR: 6.121, 95% CI: 1.623-23.086, $P = 0.007$) were statistically different. In the multivariate analysis, gal-3-INA was found to be the only independent prognostic factor (HR: 5.162, 95% CI: 1.033-25.807, $P = 0.046$).

**Discussion**

Here, we reported for the first time the relationship between the expression of galectin-3 and the prognosis of IPMN. The results of this study showed that high-galectin-3 expression and the presence of gal-3-INA were
Table 3. Pathological background of patients with invasive IPMN (n = 25)

| Pathology | Expression level of galectin-3 | Presence of gal-3-INA\(^1\) |
|-----------|-----------------------------|------------------------------|
|           | Low (n = 11) | High (n = 14) | \(P\) | + (n = 14) | − (n = 11) | \(P\) |
| Tubular   |             |               | 0.487 | 14 | 9 | 0.183 |
| Colloid   | 11          | 12            |       |       |       |       |
|           | 0           | 2             |       |       |       |       |
| Positive margin |             |               | 1.000 | 14 | 10 | 0.440 |
| +         |             |               |       |       |       |       |
|           | 11          | 13            |       |       |       |       |
| +         | 0           | 1             |       |       |       |       |
| T category |             |               | 0.227 | 5  | 3 | 1.000 |
| \(≤\) T2 | 8           | 3             |       |       |       |       |
| \(≥\) T3 | 6           | 8             |       |       |       |       |
| N category |             |               | 1.000 | 7  | 9 | 0.211 |
| 0         | 7           | 4             |       |       |       |       |
| \(≥\) 1  | 10          | 4             |       |       |       |       |
| Stage     |             |               | 1.000 | 5  | 3 | 1.000 |
| I         | 11          | 13            |       |       |       |       |
| II and III |             |               |       |       |       |       |
| 0         | 0           | 1             |       |       |       |       |
| Microscopic Lymphatic Invasion |             |               | 0.241 | 6  | 4 | 1.000 |
| −         | 6           | 5             |       |       |       |       |
| +         | 4           | 10            |       |       |       |       |
| Microscopic Vascular Invasion |             |               | 0.414 | 10 | 5 | 0.241 |
| −         | 8           | 3             |       |       |       |       |
| +         | 7           | 7             |       |       |       |       |
| Invasion into Nervous Tissue |             |               | 0.111 | 9  | 5 | 0.165 |
| −         | 8           | 3             |       |       |       |       |
| +         | 5           | 9             |       |       |       |       |

\(^1\)gal-3-INA: intranuclear accumulation of galectin-3

Fig. 2. A: Overall survival of 25 patients with invasive IPMN comparing between low and the high galectin-3 expression. There was a statistically significant difference between the groups (\(P = 0.020\)).

B: Overall survival of 25 patients with invasive IPMN comparing between patients with and without intranuclear accumulation of galectin-3.

Table 4. Univariate and multivariate analysis of prognostic factors in patients with invasive IPMN

|                      | Univariate Analysis | Multivariate Analysis |
|----------------------|---------------------|-----------------------|
|                      | HR \(^1\) | 95% CI \(^1\) | \(P\) | HR | 95% CI | \(P\) |
| galectin-3           | 2.429   | 0.622-9.002 | 0.184 |
| gal-3-INA\(^1\)      | 4.110   | 1.214-13.907 | 0.023 |
| T                    | 6.945   | 0.895-53.907 | 0.064 |
| N                    | 1.245   | 0.373-4.155 | 0.722 |
| Microscopic Lymphatic Invasion | 11.572 | 1.485-90.174 | 0.039 |
| Microscopic Vascular Invasion | 6.166 | 1.795-21.173 | 0.004 |
| Microscopic Nervous Invasion | 6.121 | 1.623-23.089 | 0.007 |

\(^1\)HR: hazard ratio, \(^1\)CI: confidential interval, \(^1\)gal-3-INA: intranuclear accumulation of galectin-3
associated with poorer prognosis in patients with invasive IPMN. In the multivariate analysis, gal-3-INA was the only independent prognostic factor. The relationship between prognosis and the status of galectin-3 expression in patients with invasive IPMN was similar to the relationship in malignancies, such as ovarian carcinoma, nasopharyngeal carcinoma, malignant melanoma, gall-bladder carcinoma, osteosarcoma, and hepatocellular carcinoma, i.e., association with poor prognosis.

The present study also highlighted the significance of gal-3-INA. Little attention has been paid to the subcellular distribution of galectin-3 in relation to patient prognosis, whereas overexpression of galectin-3 has been reported to promote various functions in tumor cells, such as anti-apoptosis, resistance to therapeutic agents, proliferation, and migration. To establish metastatic foci, tumor cells must survive conditions such as isolation from cell-cell contact or cell-matrix adhesion. This potential cancer cell development could be attained through epithelial-to-mesenchymal transition (EMT). Recently, inhibition of the kinase activity of Glycogen Synthase Kinase-3β (GSK-3β) has been shown to result in induction of EMT. Galectin-3 contains a consensus sequence of GSK-3β phosphorylation. Nuclear import/export of galectin-3 has been reported to be dependent on this phosphorylation by GSK3β. Galectin-3 has also been reported to be an important partner for the inactive form of GSK-3β to drive oncogenic transformation. On the other hand, transforming growth factor-β is a major inducer of EMT. Recently, TGF-β-induced EMT was reported to be reduced in mice deficient in galectin-3 because of its roles in fibrosis in various diseases, although the precise mechanism has not yet been elucidated. The incidence of dilatation of the main pancreatic ducts was higher in the high galectin-3 expression group. Higher galectin-3 expression might augment the incidence of duodenal dilatation due to stiffness caused by fibrosis around lesions of IPMN.

In conclusion, the presence of gal-3-INA is an independent prognostic factor for patients with invasive IPMN.

References
1) Werner, J., Fritz, S. and Büchner, M.W. (2012) Intraductal papillary mucinous neoplasms of the pancreas: a surgical disease. Nat. Rev. Gastroenterol. Hepatol. 9: 253-259.
2) Tanaka, M., Chari, S., Adsay, V., Fernandez del Castillo, C., Falconi, M., Shimizu, M., Yamaguchi, K., Yamao, K. and Matsuno, S. (2006) International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 6: 17-32.
3) Tanaka, M., Fernandez del Castillo, C., Adsay, V., Chari, S., Falconi, M., Jang, J.Y., Kimura, W., Levy, P., Pitman, M.B., Schmidt, C.M., Shimizu, M., Wolfgang, C.L., Yamaguchi, K. and Yamao, K. (2012) International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 12: 183-197.
4) Salvia, R., Fernandez-del Castillo, C., Bassi, C., Thayer, S.P., Falconi, M., Mantovani, W., Pederzoli, P. and Warshaw, A.L. (2004) Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann. Surg. 239: 678-685.
5) Sugiyama, M. and Atoymi, Y. (1996) Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. Ann. Surg. 228: 685-691.
6) Raimondo, M., Tachibana, I., Urrutia, R., Burgart, L.J. and DiMagno, E.P. (2002) Invasive cancer and survival of intraductal papillary mucinous tumors of the pancreas. Am. J. Gastroenterol. 97: 2553-2558.
7) Falconi, M., Salvia, R., Bassi, C., Zamboni, G., Talamini, G. and Pederzoli, P. (2001) Clinicopathological features and treatment of intraductal papillary mucinous tumor of the pancreas. Br. J. Surg. 88: 376-381.
8) Kanazumi, N., Nakao, A., Kaneko, T., Takeda, S., Harada, A., Inoue, S., Nagasak, T. and Nakashima, N. (2001) Surgical treatment of intraductal papillary-mucinous tumors of the pancreas. Hepatogastroenterology 48: 967-971.
9) Maire, F., Hammel, P., Terris, B., Paye, F., Scouace, J.Y., Cellier, C., Bartheil, M., O'Toole, D., Ruffat, P., Partensky, C., Cuillerier, E., Levy, P., Belghiti, J. and Ruszniewski, P. (2002) Prognosis of malignant intraductal papillary mucinous tumors of the pancreas after surgical resection. Comparison with pancreatic ductal adenocarcinoma. Gut 51: 717-722.
10) Chari, S.T., Yadav, D., Smyrk, T.C., DiMagno, E.P., Miller, L.J., Raimondo, M., Clain, J.E., Norton, I.A., Pearson, R.K., Petersen, B.T., Wiersma, M.J., Farnell, M.B. and Sarr, M.G. (2002) Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology 123: 1500-1507.
11) Schnellstorfer, T., Sarr, M.G., Nagorney, D.M., Zhang, L., Smyrk, T.C., Qin, R., Chari, S.T. and Farnell, M.B. (2008) Experience with 208 resections for intraductal papillary mucinous neoplasm of the pancreas. Arch. Surg. 143: 639-646.
12) Bassi, C., Sarr, M.G., Lillemoe, K.D. and Reber, H.A. (2008) Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. J. Gastrointest. Surg. 12: 645-650.
13) Wada, K., Kozarek, R.A. and Traverso, L.W. (2005) Outcomes following resection of invasive and noninvasive intraductal papillary mucinous neoplasms of the pancreas. Am. J. Surg. 189: 632-636.
14) Akahani, S., Nangia-Makker, P., Inohara, H., Kim, H.R., Raz, A. (1997) Galectin-3: a novel antiapoptotic molecule with a functional BH1 (NWGR) domain of Bcl-2 family. Cancer Res. 57: 5272-5276.
15) Danguy, A., Camby, J. and Kiss, R. (2002) Galectins and cancer. Biochim. Biophys. Acta. 1572: 285-293.
16) Davidson, P.J., Davis, M.J., Patterson, R.J., Ripoche, M.A., Poirier, F., Wang, J.L. (2002) Shuttling of galectin-3 between the nucleus and cytoplasm. Glycobiology 12: 329-337.
17) Lin, H.M., Pestell, R.G., Raz, A., Kim, H.R. (2002) Galectin-3
enhances cyclin D1 promoter activity through SPI and a cAMP-responsive element in human breast epithelial cells. Oncogene 21: 8001-8010.

18) Kim, M.K., Sung, C.O., Do, J.G., Jeon, H.K., Song, T.J., Park, H.S., Lee, Y.Y., Kim, B.G., Lee, J.W. and Bae, D.S. (2011) Overexpression of galectin-3 and its clinical significance in ovarian carcinoma. Int. J. Clin. Oncol. 16: 352-358.

19) Acikalin, M.F., Etiz, D., Gurbuz, M.K., Ozodogru, E., Canaz, F. and Colak, E. (2012) Prognostic significance of galectin-3 and cyclin D1 expression in undifferentiated nasopharyngeal carcinoma. Med. Oncol. 29: 742-749.

20) Brown, E.R., Doig, T., Anderson, N., Brenn, T., Doherty, V., Xu, Y., Bartlett, J.M., Smyth, J.F. and Melton, D.W. (2012) Association of galectin-3 expression with melanoma progression and prognosis. Eur. J. Cancer 48: 865-874.

21) Yang, L.P., Jiang, S., Liu, J.Q., Miao, X.Y. and Yang, Z.L. (2012) Up-regulation of galectin-3 and sambucus nigra agglutinin binding site is associated with invasion, metastasis and poor-progression of the gallbladder adenocarcinoma. Hepatogastroenterology 59: 2089-2094.

22) Zhou, X., Jing, J., Peng, J., Mao, W., Zheng, Y., Wang, D., Wang, X., Liu, Z. and Zhang, X. (2014) Expression and clinical significance of galectin-3 in osteosarcoma. Gene 546: 403-407.

23) Jiang, S.S., Weng, D.S., Wang, Q.J., Pan, K., Zhang, Y.J., Li, Y.Q., Li, J.J., Zhao, J.J., He, J., Lv, L., Pan, Q.Z. and Xia, J.C. (2014) Galectin-3 is associated with a poor prognosis in primary hepatocellular carcinoma. J. Transl. Med. 12: 273.

24) Shimamura, T., Sakamoto, M., Iino, Y., Shimada, K., Kosuge, T., Sato, Y., Tanaka, K., Sekihara, H. and Hirohashi, S. (2002) Clinicopathological significance of galectin-3 expression in ductal adenocarcinoma of the pancreas. Clin. Cancer Res. 8: 2570-2575.

25) Piantelli, M., Iacobelli, S., Almadori, G., Iezzi, M., Tinari, N., Natoli, C., Cadoni, G., Lauriola, L. and Ranelletti, F.O. (2002) Lack of expression of galectin-3 is associated with a poor outcome in node-negative patients with laryngeal squamous-cell carcinoma. J. Clin. Oncol. 20: 3850-3856.

26) Okada, K., Shimura, T., Suehiro, T., Mochiki, E. and Kuwano, H. (2006) Reduced galectin-3 expression is an indicator of favorable prognosis in gastric cancer. Anticancer Res. 26: 1369-1376.

27) Merseburger, A.S., Kramer, M.W., Hennenlotter, J., Serth, J., Kruck, S., Gracia, A., Stenzl, A. and Kuzycz, M.A. (2008) Loss of galectin-3 expression correlates with clear cell renal carcinoma progression and reduced survival. World J. Urol. 26: 637-642.

28) Yamaki, S., Fuji, T., Yajima, R., Hirakata, T., Yamauchi, S., Fujisawa, T., Tsutsumi, S., Asao, T., Yanagita, Y., Iijima, M. and Kuwano, H. (2013) Clinicopathological significance of decreased galectin-3 expression and the long-term prognosis in patients with breast cancer. Surg. Today 43: 901-905.

29) Terris, B., Blaveri, E., Crnogorac-Jurcevic, T., Jones, M., Missiaglia, E., Ruszniewski, P., Sauvanet, A. and Lemoine, N.R. (2002) Characterization of gene expression profiles in intraductal papillary-mucinous tumors of the pancreas. Am. J. Pathol. 160: 1745-1754.

30) Kobayashi, T., Shimura, T., Yajima, T., Kubo, N., Araki, K., Wada, W., Tsutsumi, S., Suzuki, H., Kuwano, H. and Raz, A. (2011) Transient silencing of galectin-3 expression promotes both in vitro and in vivo drug-induced apoptosis of human pancreatic carcinoma cells. Clin. Exp. Metastasis 28: 367-376.

31) Kao, S.H., Wang, W.L., Chen, C.Y., Chang, Y.L., Wu, Y.Y., Wang, Y.T., Wang, S.P., Nesvizhskii, A.I., Chen, Y.J., Hong, T.M. and Yang, P.C. (2014) GSK3β controls epithelial-mesenchymal transition and tumor metastasis by CHIP-mediated degradation of Slug. Oncogene 33: 3172-3182.

32) Song, S., Mazurek, N., Liu, C., Sun, Y., Ding, Q.Q., Liu, K., Hung, M.C. and Bresalier, R.S. (2009) Galectin-3 mediates nuclear β-catenin accumulation and Wnt signaling in human colon cancer cells by regulation of glycogen synthase kinase-3β activity. Cancer Res. 69: 1343-1349.

33) Mendonça, D.F., Chammas, R., Liu, F.T., Nonogaki, S., Cardoso, S.V., Loyola, A.M. and de Faria, P.R. (2012) The inactive form of glycogen synthase-3beta is associated with the development of carcinoma in gastric-3-deficient mice. Int. J. Clin. Exp. Pathol. 5: 547-554.

34) MacKinnon, A.C., Gibbons, M.A., Farnworth, S.L., Leffler, H., Nilsson, U.J., Delaine, T., Simpson, A.J., Forbes, S.J., Hirani, N., Gauldie, J. and Sethi, T. (2012) Regulation of transforming growth factor-β-driven lung fibrosis by galectin-3. Am. J. Respir. Crit. Care Med. 185: 537-546.

35) Wang, L., Friess, H., Zhu, Z., Frieger, L., Zimmermann, A., Korc, M., Berberat, PO. and Büchler M.W. (2000) Galectin-1 and galectin-3 in chronic pancreatitis. Lab. Invest. 80: 1233-1241.

36) Gebhardt, A., Ackermann, W., Unver, N. and Elsässer, H.P. (2004) Expression of galectin-3 in the rat pancreas during regeneration following hormone-induced pancreatitis. Cell Tissue Res. 315: 321-329.

37) Martínez-Martínez, E., Calvier, L., Fernández-Celis, A., Rousseau, E., Jurado-López, R., Rossoni, L.V., Jaisser, F., Zannad, S.V., Loyola, A.M. and de Faria, P.R. (2000) Galectin-1 and galectin-3 in chronic pancreatitis. Lab. Invest. 80: 1233-1241.

38) Bacigalupo, M.L., Manzi, M., Rabinovich, G.A. and Troncoso, M.F. (2012) Prognostic significance of galectin-3 and cytoplasmic cyclin D1 expression in undifferentiated nasopharyngeal carcinoma. Int. J. Clin. Oncol. 16: 352-358.

39) Li, L.C., Li, J. and Gao, J. (2014) Function of galectin-3 and its role in fibrotic diseases. J. Parmacol. Exp. Ther. 351: 336-343.