Annexin A10 Expression Is Associated With Poor Prognosis in Small Bowel Adenocarcinoma

AKIRA ISHIKAWA¹, KAZUYA KURAOKA^{1,2#}, JUNICHI ZAITSU², AKIHISA SAITO², TOSHIO KUWAI³, YOSUKE SHIMIZU⁴, TAKESHI SUDO⁴, HIROTAKE TASHIRO⁴, KIYOMI TANIYAMA⁵ and WATARU YASUI⁶

¹Institute for Clinical Laboratory, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan;

²Department of Diagnostic Pathology, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan;

³Department of Gastroenterology, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan;

⁴Department of Surgery, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan;

⁵Honorary President, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan;

⁶Department of Molecular Pathology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Abstract. *Background/Aim:* Small bowel adenocarcinoma (SBA) is a relatively rare malignant epithelial neoplasm. Thus, little is known about prognostic biomarkers of SBA. Annexin A10 (ANXA10) is a member of the annexin family. The significance of ANXA10 expression in SBA is unclear. This is the first study to examine the expression of ANXA10 in SBA. *Materials and Methods:* We immunohistochemically evaluated ANXA10 expression of SBA and studied the relationship between ANXA10 expression and clinicopathological factors. *Results:* ANXA10 expression was detected in 17 (56.7%) of 30 SBA cases and was significantly associated with poor overall survival. Univariate predictors for poor prognosis were tumour size ($p=0.017$) and ANXA10 expression ($p=0.026$). In multivariate analysis, ANXA10 expression ($p=0.038$) and tumour size ($p=0.024$) were found to be independent predictors of poor prognosis. *Conclusion:* ANXA10 could be a new prognostic biomarker for SBA.

Small bowel adenocarcinoma (SBA) is a relatively rare malignant epithelial neoplasm. The small intestine, consisting of the duodenum, jejunum, and ileum, represents 75% of the length of the gastrointestinal tract, extending from the pylorus to the ileocecal valve. Less than 5% of the total annual gastrointestinal cancer incidence occurs in the small intestine (1). The frequency of small bowel cancer is 1.2-2.3 cases per 100000 person-years (2). The most common subtype is SBA, which accounts for 30-40% of small bowel cancers (3). Many aspects are common between SBA and colorectal cancers (CRCs), including geographical correlation in incidence rates (4). Several genetic factors similar to those in CRCs, such as *TP53* (5) and *CTNNB1* (encoding β -catenin) (6), have been reported. Due to these similarities, the management of SBA has been based on that of CRCs (7). However, in contrast to CRCs, there is considerable room for improvement in the management of SBA. In a recent metaanalysis of unresectable or metastatic SBA chemotherapy, the objective response rate and the disease control rate were 18-50% and 29-87%, respectively (7). Therefore, a prognostic biomarker of SBA is required.

Annexin A10 (ANXA10) is a member of the annexin family and a calcium- and phospholipid-binding protein. Annexin family proteins are characterized by their signature feature, the annexin repeat (8), and have diverse and crucial functions in cellular and physiological processes (9, 10). In normal organs, the expression of ANXA10 is detected in the stomach, bladder, kidney, urinary bladder, and duodenum. In the duodenum, ANXA10 expression is limited to the nuclei of Brunner gland cells but is not observed in the mucosal epithelia (11).

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Correspondence to: Kazuya Kuraoka, Department of Diagnostic Pathology, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, 3-1 Aoyama, Kure 737-0023, Japan. Tel: +81 823223111, Fax: +81 823210478, e-mail: kuraoka.kazuya.vk@mail.hosp.go.jp

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Several carcinomas have been reported to express ANXA10, including carcinomas of the liver (12), gastro-intestine (11), and oesophagus (13). We have previously reported that ANXA10 is associated with the gastric phenotype of gastric cancer through the regulation of pancreatic duodenal homeobox-1 (PDX1) (14) and that ANXA10 is associated with early-stage gastric cancer (15). Previous studies have suggested that some SBA cases have been known to express gastric mucin (MUC5AC and MUC6) and have the gastric phenotype (16). However, the significance of ANXA10 expression in normal small intestine and SBA has not been investigated. This is the first study to investigate the expression of ANXA10 in SBA.

In the current study, we aimed to investigate the expression and prognostic value of ANXA10 in SBA by examining its expression by immunohistochemistry (IHC) in surgically or endoscopically resected tissue samples from 30 cases. Furthermore, we examined the correlations between the expression of ANXA10 protein and clinicopathological features. Lastly, we investigated the relationship between ANXA10 expression and prognosis of SBA cases.

Materials and Methods

Tissue samples. In this retrospective study, 30 primary SBA tissue samples were gathered from SBA patients, who underwent surgical or endoscopic resection between January 2002 and December 2019 at the Kure Medical Center and Chugoku Cancer Center (Hiroshima, Japan). Patients were observed by their physicians until their death or the date of the last documented contact. For IHC, the collected tissue samples were archival formalin-fixed and paraffin-embedded. One representative tumour block from each patient was evaluated by IHC. The tumour stage was determined according to the TNM classification system. Histological classifications were determined based on the guidelines of the Japanese Society for the Colon and Rectum due to a lack of SBA-specific guidelines. The Ethical Committee for Human Genome Research of Kure Medical Center and Chugoku Cancer Center (2019-91) approved the present study and all patient samples were obtained with consent.

Immunohistochemistry. IHC staining was performed based on previously described methods with some modifications (14, 15). For IHC evaluation, paraffin-embedded tissue samples from 30 representative blocks were cut into 4 µm-thick sections, deparaffinized, and rehydrated. IHC staining was performed using a Ventana Benchmark ULTRA auto-stainer (Ventana Medical Systems, Tucson, AZ, USA) and the labelled streptavidin-biotin peroxidase method, and signals were visualized with 3,3'-diaminobenzidine. For antigen retrieval mild and standard cell conditioning 1 buffer was used. Sections were incubated with a rabbit monoclonal anti-ANXA10 antibody (1:500, Novus Biologicals, Centennial, CO, USA, NBP1-90156) for 32 min. Endogenous peroxidase activity was not blocked. ANXA10 expression was scored in all tumours as positive or negative. The specificity of the antibody has been previously confirmed (5). The endogenous positive control was the Brunner's gland in the same section, while the negative control was fibroblasts. When >10% of

Figure 1. Annexin A10 (ANXA10) expression was detected in mouse small intestinal tumours. GEO2R analysis of six non-neoplastic and six neoplastic tissue samples from GSE111594.

tumour cells were stained, the immunostaining was regarded positive for ANXA10. Based on these rules, two surgical pathologists (A.I. and K.K.), with no knowledge of the clinical and pathologic parameters or patient outcomes, independently reviewed the immunoreactivity of each specimen.

Microarray dataset analysis. We used the GSE dataset (GSE111594) comprising six mouse intestinal tumour and six crypt cell samples, which was downloaded from the GEO database (17) and analysed using GEO2R.

Statistical analysis. A $p < 0.05$ was considered to indicate a statistically significant difference. We used Fisher's exact test to examine correlations between clinicopathological parameters and ANXA10 expression. To test the statistical differences between survival curves the log-rank test was used. Univariate and multivariate Cox regressions were tested for the associations between clinical covariates and overall survival. The hazard ratio and 95% confidence intervals were calculated from Cox proportional hazard models.

Results

ANXA10 expression was identified in mouse intestinal tumours. First, to examine the expression of ANXA10 in small intestinal tumours, we analysed the levels of ANXA10 expression in six crypt cells and six tumour cells in the Gene Expression Omnibus (GEO) database with accession no. GSE111594 using GEO2R. The ANXA10 levels were significantly higher in tumour cells than crypt cells (Figure 1). This result supported the hypothesis that ANXA10 expression, which is not expressed in normal small intestine, could be expressed in small intestinal tumours.

Table I. Patient characteristics.

All	Total 30 cases (%)
Age (years)	
Mean (range)	65.4 (61-70)
Gender	
Male	17 (56.7)
Female	13
Size (cm)	
Mean (range)	3.7 (2.5-4.9)
Site	
Duodenum	21 (70)
Ileum/Jejunum	9 (30)
pT	
pT1/2	12 (40)
pT3/4	18
pN	
pN0	21
pN1/2/3	9 (30)
Histological type	
Well differentiated tubular	16 (53)
Moderately differentiated tubular	6 (20)
Papillary (pap)	3 (10)
Mucinous (muc)	2 (6)
Lymphatic invasion (Ly)	
Ly0	19
Ly1	11 (36.7)
Vascular invasion (V)	
V0	24
V1	6 (20)
ANXA10 expression	
Positive	17 (56.7)
Negative	13

Clinicopathological features of recruited patients. To examine the clinicopathological features of SBA, we recruited 30 patients diagnosed with SBA in our institute. The clinicopathological features are summarized in Table I. The mean age was 65.4 years (range=61-70 years), and 17 (56.7%) patients were male. The mean of tumour size was 3.7 cm (range=2.5-4.9 cm). Regarding the primary tumour site, 21 (70%) were in the duodenum, and in the other 9 (30%) cases was in the ileum or jejunum. In terms of the pathological features and TNM staging, 12 (40%) cases were diagnosed with pT1 or pT2, whereas another 18 cases were pT3 or pT4. Nine (30%) cases had lymph node metastasis. Regarding the histological subtype, 16 (53%) cases were well differentiated, 6 (20%) cases were moderately differentiated, 3 (10%) cases were papillary, and 2 (6%) cases were mucinous adenocarcinoma. Lymphatic invasion and vascular invasion were observed in 11 (36.7%) and 6 (20%) cases, respectively. ANXA10 expression was detected in 17 (56.7%) cases.

ANXA10 expression in the small intestine and SBA. To investigate the clinicopathological significance of ANXA10

Table II. The relationship between ANXA10 expression and clinicopathological features in patients with small bowel adenocarcinoma.

	Annexin A10 expression		p-Value
	Positive (%)	Negative	
Age (years)			1.000
<65	10 (58)	8	
≥65	7 (58)	5	
Gender			1.000
Male	9 (60)	6	
Female	8 (53)	7	
Size (cm)			0.462
<3.7	7 (47)	8	
≥3.7	10 (67)	5	
pT			1.000
pT1/2	7 (58)	5	
pT3/4	10 (58)	8	
pN			1.000
pN0	12 (71)	9	
pN1/2/3	5 (56)	4	
V			0.672
V0	13 (54)	11	
V1	4 (67)	2	
Ly			0.462
Ly0	10 (53)	9	
Ly1	7 (64)	4	

expression, we performed IHC staining for ANXA10 in 30 SBA tissue samples, including non-neoplastic tissue. In non-neoplastic duodenal tissue, ANXA10 expression was observed in Brunner glands, as has been reported (11), but not in absorptive cells or goblet cells (Figure 2A). ANXA10 expression in Brunner glands was heterogeneous and was found in the nuclei of the gland cells (Figure 2B). No ANXA10 expression was observed in either the jejunum or ileum (Figure 2C and D). In SBA tissue, ANXA10 expression was detected in the nuclei and cytoplasm of tumour cells (Figure 2E and F). We defined immunostaining as positive if 10% of the SBA cancer cell nuclei showed visible signals, according to previous studies (14, 15). A total of 17 (56.7%) SBA samples showed ANXA10 expression. Several SBA samples demonstrated ANXA10 staining heterogeneity, and heterogeneous ANXA10 expression with no trend was observed.

Correlation between ANXA10 expression and clinicopathological features in SBA. To determine the relationship between ANXA10 staining and clinicopathologic features (Table II) we performed that Fisher's exact test, which demonstrated no significant difference between ANXA10 expression and any factors, including age ($p=1.000$), sex ($p=1.000$), size ($p=0.462$), pT ($p=1.000$), pN ($p=1.000$), V ($p=0.672$), or Ly ($p=0.462$).

Figure 2. Representative annexin A10 (ANXA10) images in non-neoplastic small intestinal mucosa and small bowel adenocarcinoma (SBA). (A, B) Immunohistochemical staining for ANXA10 in non-neoplastic duodenal mucosa. Original magnification: (A) 100 $\times$ and (B) 400 $\times$. (C, D) Immunohistochemical staining for ANXA10 in non-neoplastic jejunal mucosa. Original magnification: (C) 100 $\times$ and (D) 400 $\times$. (E, F) Immunohistochemical staining for ANXA10 in SBA. Original magnification: (E) 100 $\times$ and (F) 400 $\times$.

Correlation between ANXA10 expression and survival of SBA patients. The 5-year overall survival (OS) rate was 36.7% for ANXA10-positive cases and 82.5% for ANXA10-negative cases. ANXA10-positive SBA cases had significantly poorer survival probability than ANXA10-negative cases ($p=0.030$; Figure 3A). The 5-year disease-free survival (DFS) rate of ANXA10-positive cases was 34.0%, and that of ANXA10-negative cases was 75.5%. A marginally significant difference was observed in the 5-year DFS rate ($p=0.070$; Figure 3B). Additionally, the same examination as ANXA10 was conducted for size. The cases with tumours larger than the median 3.7 cm were categorized

as large, and those smaller than 3.7 cm were categorized as small. The 5-year OS rate was 31.5% for large tumours and 86.2% for small tumours. Large tumour SBA cases had significantly poorer survival probability than those with small tumours ($p=0.019$; Figure 3C). The 5-year DFS rates were 28.6% and 79.0% for large and small tumours, respectively. A significant difference was observed in the 5-year DFS rate ($p<0.01$; Figure 3D).

The results of the univariate and multivariate Cox proportional hazard analyses to assess ANXA10 expression as a prognostic indicator are presented in Table III. In univariate analysis, tumour size (HR=5.350; 95%CI=1.324-

Figure 3. Kaplan-Meier curves of 30 small bowel adenocarcinoma (SBA) cases. Annexin A10 (ANXA10)-positive and -negative SBA cases of (A) Overall survival (OS) and (B) disease-free survival (DFS). (C) OS and (D) DFS of large tumour and small tumour SBA cases.

35.69; $p=0.017$) and ANXA10 expression ($HR=4.926$; $95\%CI=1.194-33.28$; $p=0.026$) were associated with poor survival. In multivariate analysis, tumour size ($HR=5.000$; $95\%CI=1.215-33.72$; $p=0.024$) and ANXA10 expression ($HR=4.634$; $95\%CI=1.085-32.00$; $p=0.038$) were found to be independent predictors of survival in SBA patients.

Discussion

In the current study, we analysed the significance and expression of ANXA10 in SBA. To our knowledge, this is the first study that demonstrates the localization of ANXA10 in the small intestine and examines its significance in SBA.

A previous study has reported that, in non-neoplastic tissue, duodenal ANXA10 expression was found in the Brunner glands (11). Consistently, the expression of ANXA10 was limited to the nuclei of Brunner gland cells in the small intestine. There has been no report of ANXA10 expression in SBA. Organs close to the small intestine have been reported

to be positive in 46-74.6% of gastric cancers (11, 14, 18, 19) and 11-17% of CRCs (20, 21). In particular, ANXA10 expression was observed more frequently (up to 87.5%) in CRCs of the gastric phenotype than in conventional CRCs (20-22). Therefore, some SBAs with the gastric phenotype may have different carcinogenic pathways than other CRCs.

In the present study, univariate and multivariate analyses showed that large tumour size and ANXA10 expression correlated with OS and acted as an independent prognostic classifier of patients with SBA. In view of tumour size, a size ≥ 5 cm has been suggested to influence survival time (23). However, the most interesting observation was the significance of ANXA10 expression in SBA. Previous reports have shown that ANXA10 is an independent prognostic factor in several carcinomas: hepatocellular carcinoma (12), cholangiocarcinoma (24), ovarian cancer (25), thyroid cancer (26), and early gastric cancers (15). These results suggest that ANXA10 immunostaining is a clinically significant modality to predict survival of SBA patients.

Table III. Univariate and multivariate Cox regression analyses of ANXA10 expression and survival of small bowel adenocarcinoma patients.

Features	Univariate analysis		Multivariate analysis	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Age				
<65	1 (ref.)	0.571		
≥65	1.432 (0.400-5.166)			
Size		0.017		0.024
<3.7 cm	1 (ref.)		1 (ref.)	
≥3.7 cm	5.350 (1.324-35.69)		5.000 (1.215-33.72)	
Gender		0.196		
Female	1 (ref.)			
Male	2.414 (0.067-11.26)			
pT		0.122		
pT1/2	1 (ref.)			
pT3/4	2.978 (0.740-19.83)			
pN		0.186		
pN0	1 (ref.)			
pN1/2/3	2.343 (0.650-8.453)			
V		0.064		
V0	1 (ref.)			
V1	3.707 (0.918-13.56)			
Ly				
Ly0	1 (ref.)	0.093		
Ly1	2.942 (0.831-11.62)			
ANXA10 expression				
Negative	1 (ref.)	0.026	1 (ref.)	0.038
Positive	4.926 (1.194-33.28)		4.634 (1.085-32.00)	

Regarding the association between ANXA10 expression and clinicopathological features, no correlation was detected between ANXA10 expression and other clinicopathological features despite survival significance. In previous studies, ANXA10 expression has been associated with tumour stage, lymph node metastasis, and distant metastasis in gastric cancers (14, 19) and with gender, tumour stage, tumour location, tumour differentiation, and tumour histology in CRCs (21, 22). In SBA, similar relationships are hypothesized with other gastrointestinal cancers, but further study with larger numbers of cases is needed to investigate their effects on tumour progression.

The most significant limitations in the current study are that this is a single institute study and the number of cases is small. However, given the fact that SBA is a very rare disease (1), our analysis provides new evidence for ANXA10 involvement in the pathogenesis of SBA. Another limitation of this study is that the specific role of ANXA10 in SBA was not examined. The function of ANXA10 has been reported in several organs (13, 14, 20, 21). In CRCs, ANXA10 expression has been correlated with microsatellite instability (21) and involves BRAF mutation and CpG island methylation (20). In

oesophageal cancer, ANXA10 promotes cell proliferation through phosphorylation of Akt and Erk1/2 (13). In fact, we have previously reported that ANXA10 is involved in the gastric phenotype *via* PDX1 in advanced gastric cancer (14). As with gastric cancer, there are some SBAs that have gastric phenotype (27), and the role of ANXA10 may be different in each phenotype. Identification of ANXA10 downstream signalling will further improve the understanding of the basic biology of ANXA10.

In conclusion, we demonstrated the clinical significance of ANXA10 in SBA patients. ANXA10- positive patients have significantly poor prognosis, and the expression status of ANXA10 is an independent prognostic marker. ANXA10 immunostaining could be a new prognostic indicator for SBA patients.

Conflicts of Interest

The Authors state that there are no conflicts of interest in relation to this study.

Authors' Contributions

AI designed the study. TK, YS, HT, and TS collected and analysed the patient clinical data. AI, KK, JZ, AS, and KT performed the experiments and collected and analysed the data. AI, KK, TK, YS, TS, HT, KT, and WY interpreted and analysed the results. AI, KK, and WY drafted and edited the manuscript. All Authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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