**Introduction**

Gastric cancer is a major cause of cancer-related death in the world. Although the incidence of gastric cancer is slowly declining in the United States and most other countries, including Japan, that of gastric cancer remains very high in Eastern Asia. The mortality rate as well as the incidence rate of gastric cancer are continuously decreased in both males and females due to the decrease of *Helicobacter pylori* infection and the contribution of the endoscopic screening. Nevertheless, the prognosis remains poor in advanced stage or recurrent gastric cancer cases. For those patients, in addition to conventional chemotherapies, molecularly targeted agents, such as trastuzumab targeting epidermal growth factor receptor 2 (HER2), panitumumab targeting epidermal growth factor receptor (EGFR), and ramucirumab targeting vascular endothelial growth factor receptor 2 (VEGFR2) are used and showing significant therapeutic benefit. However, therapeutic resistance was frequently occurred during the treatment and imposed a significant problem for the patient with gastric cancer.

**Abstract**

Gastric cancer is a leading cause of death worldwide. Although several therapeutic agents have been developed and showed positive efficacy for patients with gastric cancer, drug resistance remains severe problem during treatment. AT-rich interactive domain 1A (ARID1A) and annexin A1 (ANXA1) have a pivotal role in gastric tumorigenesis and reported as useful predictive or prognostic biomarkers. Previous study revealed that loss of ARID1A confers resistance to drugs that target the HER2/Pi3K/mTOR pathway in breast cancer through activation of AKT via upregulation of ANXA1. Elevated ANXA1 levels are important for trastuzumab resistance and ANXA1 expression is inversely correlated with ARID1A levels in HER2-positive breast cancer. While trastuzumab is also used in HER2-positive gastric cancer, the expression status between ARID1A and ANXA1 in gastric cancer has yet to be determined. Here, we investigated both ARID1A and ANXA1 expressions by immunohistochemical staining in the test (n = 200) and validation (n = 220) cohorts of gastric cancer. Our results revealed that the inverse correlation between ARID1A and ANXA1 was not exist in patients with gastric cancer. The mRNA microarray analysis, which identified ARID1A-regulated genes in HER2-positive gastric cancer cells, revealed that ANXA1 was not induced by ARID1A knockdown. The present study suggested that the molecular relationship between ARID1A and ANXA1 is different in gastric cancer from in the breast cancer that ANXA1 serves as a predictive biomarker for trastuzumab-based treatment. Our results prompt a further study into the investigation of functional role of ARID1A and ANXA1 in gastric cancer.

**Keywords:** ARID1A, ANXA1, gastric cancer, trastuzumab, drug resistance

Correspondence to: Motonobu Saito, Department of Gastrointestinal Tract Surgery, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan. E-mail: moto@fmu.ac.jp
of annexin A1 (ANXA1)\(^{9}\). ANXA1 is calcium-dependent phospholipid-linked protein and upregulated and has a significant role of gastric tumorigenesis\(^{10}\). Previous study also reported that low ANXA1 expression may serve as a predictive biomarker for positive efficacy of trastuzumab in patients with HER2-positive breast cancer\(^{9}\). This was indicated that patients with high levels of ANXA1 may benefit from combining trastuzumab with agents that target the PI3K/AKT pathway, which warrants further exploration in patients with gastric cancer. However, the expression status between ARID1A and ANXA1 in gastric cancer has yet to be determined.

In the present study, we evaluated the expression of ARID1A and ANXA1 by immunohistochemical (IHC) staining in an independent two cohorts (n = 200 and n = 220) of surgically resected gastric cancer. We then aimed at implicating the loss of ARID1A induce ANXA1 expression in gastric cancer.

**Materials and methods**

**Clinical samples of patients.**

A total of 420 surgical specimens obtained from gastric cancer patients who had undergone surgical resection at Fukushima Medical University Hospital between January 1991 and December 2014 were used for the experiments. All patients were recruited in a previous our study\(^{8}\). The test cohort consisted of 200 patients recruited between 2002 and 2014 and the validation cohort consisted of 220 patients recruited between 1991 and 2001. Information regarding age, sex, TNM stage (the 7th classification), and pathological diagnosis, including lymphatic and venous invasion, were retrospectively collected. The carcinomas at the time of primary tumor resection were staged according to the UICC classification. This study was approved by the ethics committee of Fukushima Medical University.

**IHC staining and evaluation.**

IHC staining was carried out on paraffin-embedded histological sections (4 μm thick) using a polymer peroxidase method. Briefly, after deparaffinization and rehydration, the sections were treated with 0.3% hydrogen peroxide in methanol for 30 min to block endogenous peroxidase activity. After being rinsed in PBS, the sections were incubated with anti-ARID1A antibody (#12354, D2A8U, 1:500 dilution, Cell signaling Technology, Danvers, MA, USA) and anti-ANXA1 antibody (clone 29, BD Biosciences, 1:1000, San Jose, CA, USA) at 4°C overnight. A further wash in PBS was followed by treatment with a peroxidase-labeled polymer, conjugated to goat anti-rabbit immunoglobulins (ENVision+kit; Dako), as the secondary antibody for 30 min at room temperature. The staining was visualized with diaminobenzidine, followed by counterstaining with hematoxylin. Expression of these proteins was evaluated as positive when the nucleus of the cancerous tissue and the total field of view were observed at 400× magnification. Specimen staining was evaluated by investigators blinded to the origin of samples and clinical outcomes. Evaluation for ARID1A expression was performed as previously described\(^{8}\) and for ANXA1 expression was performed as previously described\(^{8}\).

**Small interfering RNA (siRNA) transfection.**

This was performed in a previous our study\(^{8}\). Knockdown experiments were performed using siRNA oligos for ARID1A (s15784 and s15785, Thermo Fisher Scientific, Inc. Waltham, MA, USA) and included two target-specific siRNAs and a control siRNA (ID, Thermo Fisher Scientific, Inc.) according to the manufacturer’s protocol. The gastric cancer cell lines NCI-N87 (N87) used in the present study was originally obtained from the American Type Culture Collection (Manassas, VA, USA). The cells were cultured in the RPMI-1640 medium (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany). The monolayer cells were maintained in a 37°C incubator with 5% CO2 observed regularly under a light microscope (magnification, x40) and subcultured when they reached 80–90% confluency. The day prior to transfection, N87 cells were seeded at a density of 15x10⁵ cells/well in a 6-well plate. Transfection using Lipofectamine RNAiMAX (Thermo Fisher Scientific, Inc.) with a final concentration of 10 nM siRNA was performed when the cell density was 30–50% in the 6-well plates and cells were subsequently incubated at 37°C for 48 h.

**Microarray analysis.**

This was performed in a previous our study\(^{8}\). Total RNA was isolated from N87 cells using TRIzol (Thermo Fisher Scientific, Inc.) according to the manufacture’s protocol. Microarray analysis was performed using Agilent platform (SuperPrint G3 Human GE Ver 3.0 [Design ID: 72363]) was used to investigate gene alterations. Data were normalized and analyzed using GeneSpring software (Agilent). The fold change in expression was defined as the ratio of expression in ARID1A knock-down cells to that in control (scrambled siRNA). The raw microarray data are deposited in the Gene Expression Omnibus at the National Center for Biotechnology Information (GSE118273).

**Statistical Analysis.**

Fisher’s exact test were performed by GraphPad Prism.
Table 1  Clinicopathological characteristics of gastric cancer

|                      | Test cohort n=200 | Validation cohort n=220 |
|----------------------|------------------|-------------------------|
| Age-year             |                  |                         |
| Mean                 | 67.1             | 64.5                    |
| Range                | 30-90            | 29-91                   |
| Gender-no. (%)       |                  |                         |
| Male                 | 138 (69)         | 155 (70)                |
| Female               | 62 (31)          | 65 (30)                 |
| Histological type-no. (%) |             |                         |
| Differentiated       | 107 (54)         | 121 (55)                |
| Undifferentiated     | 93 (46)          | 99 (45)                 |
| TNM Stage-no. (%)    |                  |                         |
| I                    | 105 (53)         | 107 (49)                |
| II                   | 32 (16)          | 36 (16)                 |
| III                  | 42 (21)          | 52 (24)                 |
| IV                   | 21 (10)          | 25 (11)                 |
| Depth of invasion-no. (%) |          |                         |
| T1                   | 96 (48)          | 75 (34)                 |
| T2                   | 22 (11)          | 83 (38)                 |
| T3                   | 26 (13)          | 54 (25)                 |
| T4                   | 56 (28)          | 8 ( 4)                  |
| LN metastasis-no. (%)|                  |                         |
| Positive             | 85 (43)          | 116 (52)                |
| Negative             | 115 (57)         | 104 (48)                |
| Lymphatic invasion-no. (%) |       |                         |
| Present              | 123 (62)         | 186 (85)                |
| Absent               | 77 (38)          | 34 (15)                 |
| Venous invasion-no. (%) |                |                         |
| Present              | 117 (59)         | 164 (75)                |
| Absent               | 83 (41)          | 56 (25)                 |
| ARID1A expression-no. (%) |            |                         |
| Positive             | 161 (81)         | 180 (82)                |
| Negative             | 39 (19)          | 40 (18)                 |
| ANXA1 expression-no. (%) |             |                         |
| Positive             | 91 (45)          | 98 (45)                 |
| Negative             | 109 (55)         | 122 (55)                |

Results

**ARID1A and ANXA1 protein expression in gastric cancer**

We have evaluated ARID1A expression by IHC staining in two independent gastric cancer cohorts (Table 1). In this study, we added IHC staining for ANXA1 in these test and validation cohorts (Fig. 1). ARID1A expression was positive in 161 cases (80.5%) and negative in 39 cases (19.5%) in the test cohort, whereas that was positive in 180 cases (81.8%) and negative in 40 cases (18.2%) in the validation cohort. On the other hand, ANXA1 expression was positive in 91 cases (45.5%) and negative in 109 cases (55.5%) in the test cohort, whereas that was positive in 161 cases (80.5%) and negative in 39 cases (19.5%) in the validation cohort. Although the results were opposite of our hypothesis, it was reported that ARID1A and ANXA1 have a pivotal work in tumorigenesis and also could work as predictive or prognostic biomarkers in gastric cancer. Although the results were opposite of our hypothesis, it was reported that ARID1A and ANXA1 have a pivotal work in tumorigenesis and also could work as predictive or prognostic biomarkers in gastric cancer. In the present study, we have evaluated both ARID1A and ANXA1 expressions in gastric cancer by IHC staining and found no correlations between these expressions. Although the results were opposite of our hypothesis, it was reported that ARID1A and ANXA1 have a pivotal work in tumorigenesis and also could work as predictive or prognostic biomarkers in gastric cancer. In fact, ARID1A has a tumor suppressor function and inactivating mutations of ARID1A is frequently detected in gastric cancer. We reported that negative expression of ARID1A by IHC staining was detected about 20% of patients with gastric cancer and associated with adverse clinicopathological factors, such as lymphatic invasion and lymph node metastasis.

**ANXA1 was not induced ARID1A loss in gastric cancer**

We further investigated whether ARID1A loss induced ANXA1 expression in gastric cancer or not. We have previously performed microarray analysis to identify ARID1A-regulated genes in gastric cancer and profiled RNA isolated from HER2-positive N87 gastric cancer cells, in which ARID1A expression was knocked down by two different siRNAs against ARID1A. This analysis revealed that 162 transcripts were more than 2-fold upregulated and 142 transcripts were more than 2-fold downregulated in ARID1A knockdown cells compared to the control cells. We then focused on ANXA1 family genes, including ANXA1 (Table 3). We found that ANXA1 was downregulated in ARID1A knockdown cells compared to the control cells and the most upregulated gene was ANXA6, whereas the most downregulated gene was ANXA11 in our experiment (Fig. 2).

Discussion

In the present study, we have evaluated both ARID1A and ANXA1 expressions in gastric cancer by IHC staining and found no correlations between these expressions. Although the results were opposite of our hypothesis, it was reported that ARID1A and ANXA1 have a pivotal work in tumorigenesis and also could work as predictive or prognostic biomarkers in gastric cancer. In fact, ARID1A has a tumor suppressor function and inactivating mutations of ARID1A is frequently detected in gastric cancer. We reported that negative expression of ARID1A by IHC staining was detected about 20% of patients with gastric cancer and associated with adverse clinicopathological factors, such as lymphatic invasion and lymph node metastasis. We also reported that ARID1A has a role of useful prognostic biomarker that negative expression of ARID1A was associated with poor overall survival in undifferentiated cases, particularly early-stage cases in gastric cancer. ANXA1 is also known to play a critical role in gastric cancer development. We reported that gastric cancer cases with positive ANXA1 expression by IHC staining were statistically significantly different in the test and validation cohorts. A positive expression of ANXA1 was not significantly found in ARID1A negative cases in the test cohort (P = 0.475) (Table 2). Similar result was found in the validation cohort that positive expression of ANXA1 was not significantly associated with ARID1A negative cases (P = 0.080). These results suggested that negative expression of ARID1A had no association with positive expression of ANXA1 in patients with gastric cancer.
Table 2  Correlation between ANXA1 and ARID1A IHC staining in gastric cancer

|                      | Test cohort (n=200) | Validation cohort (n=220) |
|----------------------|---------------------|---------------------------|
|                      | ARID1A              | ARID1A                    |
|                      | Total               | Total                     |
|                      | positive (n=161)    | positive (n=180)          |
|                      | negative (n=39)     | negative (n=40)           |
| ANXA1-no. (%) positive | 91                  | 98                        |
| ANXA1-negative       | 109                 | 122                       |
|                      | 71 (44)             | 75 (43)                   |
|                      | 20 (51)             | 23 (58)                   |
|                      | 19 (49)             | 17 (42)                   |
|                      | 0.475               | 0.080                     |

Table 3  Differentially expressed ANXA family genes in ARID1A knockdown cells

| ProbeName | Annotation | Normalized Data | Log2 Fold Change |
|-----------|------------|-----------------|------------------|
| A_23_P94501 | ANXA1 | 8.28016 8.282143 8.018124 | -0.001982689 -0.26203632 -0.130026816 down |
| A_23_P146644 | ANXA2 | 9.254221 9.499226 9.390768 | 0.24500465 0.13654709 0.1907587 up |
| A_32_P148345 | ANXA2 | 4.3664274 4.4401307 4.291807 | 0.07370329 -0.07462025 -0.00045848 down |
| A_24_P204244 | ANXA2P1 | 6.806817 6.9013524 6.7120466 | 0.09453535 -0.09477043 -0.00011754 down |
| A_24_P323114 | ANXA2P3 | 2.416422 2.4860435 2.27493 | 0.06962156 -0.14149189 -0.03593516 down |
| A_33_P3299279 | ANXA2R | 0.9196527 0.78900623 0.8052798 | -0.13095903 -0.06968546 -0.10322245 down |
| A_23_P121716 | ANXA3 | 6.175543 6.0250373 5.912876 | 0.13050554 -0.2626667 -0.20658612 down |
| A_22_P00025049 | ANXA4 | 2.594777 -2.1610718 -2.253957 | 0.43370533 0.34082007 0.3872627 up |
| A_23_P69720 | ANXA5 | 4.1440868 4.1679854 4.086397 | 0.023976803 -0.057611465 -0.01681733 down |
| A_23_P353014 | ANXA6 | -2.520902 -2.167019 -1.9402494 | 0.3557929 0.5868525 0.4672227 up |
| A_23_P86570 | ANXA7 | 2.7317159 2.9121258 2.983778 | 0.1841429 0.24666214 0.215402365 up |
| A_33_P3329949 | ANXA7 | 4.3919964 4.4868197 4.628479 | 0.09482336 0.23648262 0.16565299 up |
| A_32_P103549 | ANXAB1 | 4.4476626 4.547933 4.3950434 | 0.10007048 -0.052819252 0.032520614 up |
| A_23_P103617 | ANXA9 | 3.8012094 4.1160264 3.861889 | 0.31481695 0.060679436 0.18748193 up |
| A_23_P35399 | ANXA11 | 5.782648 6.384605 5.957075 | 0.601958648 0.17442030 0.388191935 up |
| A_33_P3356255 | ANXA11 | -1.3169742 -0.9516187 -1.2905335 | 0.3653555 0.02644062 0.19589806 up |
| A_32_P150632 | ANXA11 | -1.0636659 -1.5953317 -1.0481386 | -0.5316658 0.015527248 -0.258069276 down |

Fig. 1  Representative immunohistochemical staining for ARID1A and ANXA1 in gastric cancer. Positive and negative stain of ARID1A and ANXA1 in tumorous tissue. Scale bars = 100 µm.
associated with lymphatic invasion, venous invasion, and lymph node metastasis\textsuperscript{12}. In addition, upregulated ANXA1 expression may play a critical role in 5-FU resistance, affecting worsened cancer outcome and poor survival\textsuperscript{14}.

We revealed that downregulation of \textit{ARID1A} by siRNA most significantly induced \textit{ANXA6} expression among \textit{ANXA} families. To date, the role of \textit{ANXA6} is controversial that exhibits dual functions in various cancers\textsuperscript{15}. While the expression of \textit{ANXA6} was found to be downregulated by promoter methylation in gastric cancer cell lines, demethylation treatment may restore that of \textit{ANXA6}\textsuperscript{15}. The reason of \textit{ANXA6} upregulation by \textit{ARID1A} silencing is unknown, but it would be the necessity of further investigation focusing on the role of methylation in the promoter of the \textit{ANXA6} in gastric cancer. On the other side, our study also demonstrated that downregulation of \textit{ARID1A} by siRNA did not directly induce \textit{ANXA1} expression in HER2-positive gastric cancer cells. While loss of \textit{ARID1A} directly impact the transcription machinery that \textit{ANXA1} RNA and protein expressions were induced by \textit{ARID1A} loss in breast cancer cell lines, this molecular regulation was not confirmed in gastric cancer cell line. In breast cancer, \textit{ARID1A} suppression activates \textit{ANXA1} expression leading to AKT activation, resulting trastuzumab resistance in HER2-positive cases. In clinical, drug resistance against trastuzumab is frequently occurred during the treatment of HER2-positive gastric cancer. However, our results suggested that trastuzumab resistance may be occurred by another route of HER2-positive gastric cancer.

While \textit{ANXA1} serves as a predictive biomarker for trastuzumab, \textit{ARID1A} could be a therapeutic target by synthetic lethal manner using EZH2 inhibitors, PARP inhibitors or ATR inhibitors\textsuperscript{16-18}. Because most of \textit{ARID1A} mutations is inactivating mutations, \textit{ARID1A} itself is hard to be a direct therapeutic target\textsuperscript{13}. Among several inhibitors that are developed using synthetic lethal approach, EZH2 inhibitors are mostly expected to show a positive efficacy and the response to EZH2 inhibitors often correlates with gain-of-function mutations in \textit{EZH2}\textsuperscript{16}. Consisting with a previous report that EZH2 was overexpressed in many solid cancers\textsuperscript{19}, we confirmed that EZH2 was positively expressed in ARID1A loss gastric cancer in our cohort, suggesting that there is a therapeutic opportunity using EZH2 inhibitors for the patient with ARID1A loss gastric cancer.

In conclusion, the current study suggested that ARID1A loss induce ANXA1 expression, working as a predictive biomarker for trastuzumab-based treatment.
in breast cancer, but not in gastric cancer. Our results prompt the further study into the investigation of functional role and into the development of targeted therapy of ARID1A and ANXA1 in gastric cancer.\textsuperscript{20, 21}

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