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CUB Domain-containing Protein 1 (CDCP1) Is Down-regulated by Active Hexose-correlated Compound in Human Pancreatic Cancer Cells

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Abstract. *Background/Aim: We have previously reported that treatment of pancreatic cancer cells with active hexose-correlated compound (AHCC), an extract of a basidiomycete mushroom, decreases the levels of tumor-associated proteins including heat-shock protein 27 (HSP27), heat shock factor 1 (HSF1) and sex-determining region Y-box 2 (SOX2). The transmembrane glycoprotein, CUB domain-containing protein 1 (CDCP1) has been reported to be up-regulated in various cancers, and be associated with invasion and metastasis. The aim of this study was to examine the effect of AHCC on the expression of CDCP1 in KLM1-R cells. Materials and Methods: Gemcitabine-resistant pancreatic cancer cells (KLM1-R) were treated with AHCC (10 mg/ml) for 48 h. Western blot analysis of cell extracts with anti-CDCP1 or anti-actin antibodies was performed to assess the expression of CDCP1. Results: Expression of CDCP1 was reduced by AHCC treatment of KLM1-R cells, whereas expression of actin was not affected. The ratio of intensities of CDCP1/actin in AHCC-treated KLM1-R cells was significantly suppressed ($p<0.05$) compared to untreated cells. Conclusion: AHCC down-regulated CDCP1 expression and inhibited the malignant progression of pancreatic cancer cells.*

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Although molecular diagnostics and therapeutics for various cancers have been developed, pancreatic cancer still shows a poor prognosis (a 5-year survival rate of less than 5%). This very poor prognosis arises from its aggressiveness and lack of early diagnosis and effective therapies (1). At present, gemcitabine is clinically the most effective chemotherapeutic drug for pancreatic cancer (2). However, the median survival time of patients treated with gemcitabine is only half a year (3). Therefore, novel effective therapeutic agents for pancreatic cancer have to be developed.

Active hexose-correlated compound (AHCC) is derived from the basidiomycete mushroom *Lentinula edodes*. AHCC is composed of polysaccharides, amino acids, minerals and lipids enriched in α 1,4-glucans. So far AHCC has been reported to have immunomodulatory, anti-tumor, and anti-stress effects *in vivo* (4-6). We have previously investigated the direct effect of AHCC on cancer cells *in vitro*. The results showed that *in vitro* AHCC-treatment of KLM1-R cells down-regulated HSP 27, HSF1, and SOX2 (7-9). Our previous studies have shown that HSP27 is strongly related with gemcitabine-resistance in pancreatic cancer cells (10-13). Also, we have shown that SOX2, which has been reported to prompt migration and invasion (14, 15), was overexpressed in malignant progressive fibrosarcoma clone cells compared to parental regressive clone cells (16). These results suggested that AHCC suppresses the factors

associated with chemo-resistance and malignant progression. In addition, they suggested that AHCC down-regulates other proteins which play important roles in tumor malignant progression. In this study the effect of AHCC-treatment on the expression of CUB domain-containing protein 1 (CDCP1) was examined.

CDCP1 is a transmembrane glycoprotein that has been reported to be highly expressed in various cancers, and to be associated with prognosis, invasion, metastasis and anoikis-resistance in cancer cells (17-23).

In this study, the effects of *in vitro* treatment of AHCC on the expression of CDCP1 were examined in KLM1-R cells by using western blotting.

Materials and Methods

Cancer cell line and conditions. The KLM1-R pancreatic cancer cell line is gemcitabine-resistant. It has been established at the Department of Surgery and Science, Kyushu University Graduate School of Medical Science and derived from the gemcitabine-sensitive pancreatic cancer cell line KLM1, that was exposed to gemcitabine. The cells were kept in RPMI-1640 medium supplemented with 10% fetal bovine serum (inactivated at 56˚C for 30 min), 2 mM L-glutamine, 1.5 g/l sodium bicarbonate, 10 mM *N*-2-hydroxyehylpiperazine-*N*'-2-ethanesulfonic acid (HEPES), and 1.0 mM sodium pyruvate, in a CO_2 incubator.

Agents. AHCC was kindly provided by the Amino Up Chemical Co., Ltd. (Sapporo, Japan), and it was dissolved in RPMI-1640 medium and filter-sterilized before *in vitro* use.

Sample preparation. The KLM1-R cells were incubated for 48 h with or without AHCC (10 mg/ml). Then the cells were homogenized in ice-cold lysis buffer [50 mM Tris-HCl, pH 7.5, 165 mM sodium chloride, 10 mM sodium fluoride, 1 mM sodium vanadate, 1 mM phenyl methyl sulfonyl fluoride, 10 mM ethylendiaminetetra-acetic acid, 10 μg/ml aprotinin, 10 μg/ml leupeptin, and 1% nonylphenocypolyehoxylethanol-40], and centrifuged at 15,000 × *g* for 30 min at 4˚C. The supernatant was collected and used for further experiments.

Western blot analysis. Fifteen μg of protein were used in western blot analysis. Pre-cast gels (4-20% gradient polyacrylamide gels; Mini-PROTEAN TGX Gels, Bio-Rad, Hercules, CA, USA) were used for sodium dodecylsulphate-polyacrylamide gel electrophoresis (SDS-PAGE). The separated protein bands were transferred onto polyvinylidene difluoride membranes (Immobilon-P; Millipore, Bedford, MA, USA). Blocking was done with Tris-buffered saline (TBS) containing 5% skimmed milk for 1h at room temperature. The primary antibodies used were: rabbit monoclonal antibody against CDCP1 (#4115 1:1,000, CST, Beverly, MA, USA) and goat polyclonal antibody against actin (1:200, Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA). Membranes were incubated with each primary antibody overnight at 4˚C, and after washing three times with TBS containing 0.05% Tween-20, were further incubated with secondary antibodies conjugated with horseradish peroxidase (Jackson Immuno Research Laboratories Inc., West Grove, PA, USA) for 1 h. Bands of CDCP1 and actin were visualized by an enhanced chemiluminescence system (ImmunoStar Long Detection; Wako, Osaka, Japan) and LAS-1000 Pro (Fujifilm Corporation, Tokyo, Japan). Intensities of bands of CDCP1 and actin were quantified by using the Multi Gauge ver. 3.0 software (Fujifilm Corporation).

The ratio of intensity of CDCP1 to actin in AHCC-treated or untreated KLM1R cells from two independent experiments were calculated.

Results

Since CDCP1 has been reported to be over-expressed in many types of cancers and be associated with invasion and metastasis, the effect of AHCC on the expression of CDCP1 in KLM1-R cells treated with or without AHCC was examined by western blot analysis. AHCC-treatment suppressed the expression of CDCP1, but did not suppress the levels of actin (Figure 1). The ratio of intensities of CDCP1/actin in KLM1-R cells treated with or without AHCC (10 mg/ml) were 1.442±0.791 and 3.148±2.260, respectively. The *p*-value of CDCP1/actin between AHCC-treated and untreated KLM1-R cells was 0.037 ($p<0.05$) (Figure 2).

Discussion

The present study showed that AHCC down-regulated the expression of CDCP1 in gemcitabine-resistant pancreatic cancer KLM1-R cells, but it did not affect actin levels.

CDCP1 is a transmembrane glycoprotein which has been reported to be up-regulated in many kinds of cancer tissues and cells (24-26). It has been suggested that CDCP1 plays important roles in cancer invasion and metastasis (21, 27, 28).

CDCP1 was shown to modulate cell-substratum adhesion and motility in colon cancer cell lines (29). Knockdown of CDCP1 in pancreatic cancer cells resulted in up-regulation of E-cadherin and down-regulation of N-cadherin, indicating that CDCP1 suppresses the epithelial phonotype and increases mesenchymal phenotype in cancer cells (30). Furthermore, it has been shown that CDCP1 functions as an essential regulator of MT1-MMP-mediated invasion and invadopodia-mediated invasion of cancer cells (31).

Some groups reported the relationship between CDCP1 and prognosis of cancer patients. Glioblastoma is one of the most aggressive tumors among the malignant brain tumors showing strong invasiveness, recurrence and very poor prognosis. Varghese *et al*. reported that the expression of some survival kinase genes including CDCP1 was associated with recurrence-related prognosis (32). He *et al*. reported that an increased CDCP1 expression was correlated with poor disease-free and overall survival in patients with ovarian clear cell carcinoma (33). Chou *et al*. identified CDCP1 as a useful prognostic factor for patients with colorectal cancer (34). Based on these reports, it is concluded that it is very important to regulate CDCP1 for the treatment of aggressive cancer cells.

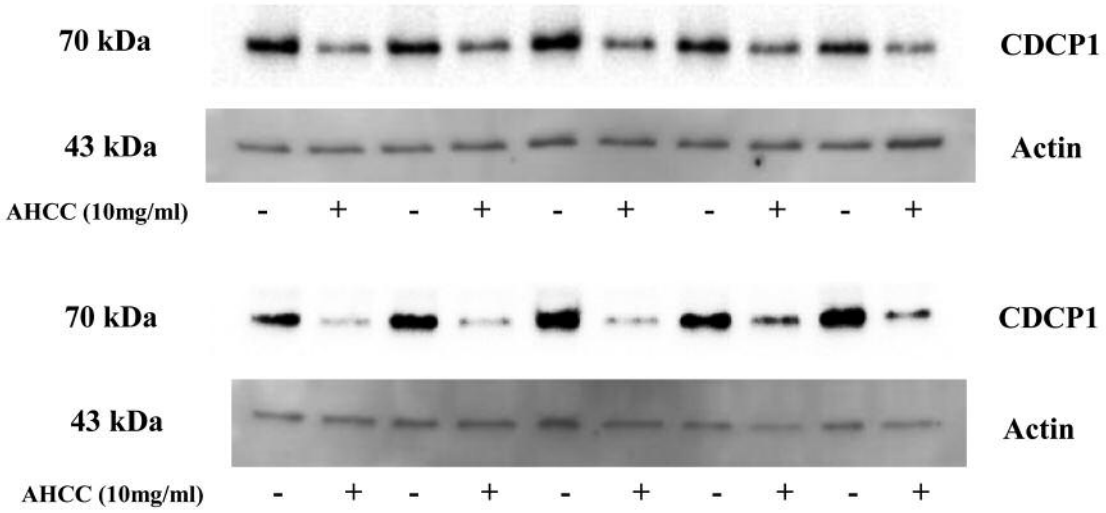

Figure 1. *Western blot analysis of CDCP1 and actin in active hexose correlated compound (AHCC) treated (10 mg/ml) or untreated (0 mg/ml) pancreatic cancer KLM1-R cells. The protein expression of CDCP1 (bands of 70 kDa) was reduced by AHCC-treatment in KLM1-R cells compared to control untreated KLM1-R cells. On the other hand, protein expression of actin (bands of 43 kDa) did not change significantly.*

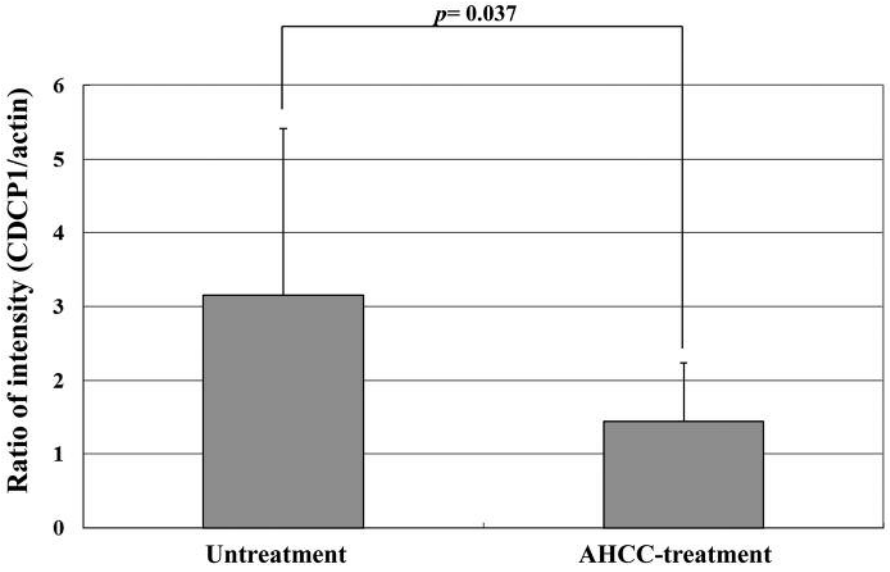

Figure 2. *The ratio of the intensities of the CDCP1/actin bands in KLM1-R cells. This graph shows the ratio of the intensities of CDCP1 protein to actin protein bands in AHCC-treated or untreated KLM1-R cells. The ratio of CDCP1/actin in KLM1-R cells was significantly reduced by AHCC treatment in vitro ($p<0.05$ by the Student's t-test). A value of $p<0.05$ was considered statistically significant (n=10).*

Chemo-resistance of cancer cells is a troubling issue in the treatment of cancer patients. In our studies aimed to identify key molecules playing important role on the induction of gemcitabine-resistance, HSP27 was shown to be an important protein involved in gemcitabine-resistance (10-13). However, to find out additional molecules related to chemo-resistance still need to be identified. Sandercock *et al*. reported that anti-CDCP1 antibody significantly enhanced the efficacy of cisplatin in a patient-derived non-small cell lung cancer xenograft model (35). Alajati *et al*. reported that CDCP1 is related not only to chemo-resistance, but also to trastuzumab resistance. They showed that CDCP1 bound to

HER2 through its intracellular domain and increased HER2 interaction with the non-receptor tyrosine kinase c-SRC led to trastuzumab resistance (36). From these reports and our recent studies, it is suggested that AHCC can be used against chemo-resistance and molecular-targeted agent-resistance cancers, since AHCC suppresses both HSP27 and CDCP1.

Several groups suggested CDCP1 as a target for cancer therapy. Harrington *et al*. showed that *in vitro* silencing of CDCP1 suppressed migration and non-adherent cell growth of high-grade serous ovarian cancer cells. Furthermore, in patient-derived xenograft mouse models, blocking CDCP1 with antibodies resulted in effective suppression of tumor growth (37). *In vitro* and *in vivo* experiments using RG7287, an activating anti-CDCP1 antibody, also suggested CDCP1 as a therapeutic target on cancer cells. The treatment with RG7287 resulted in down-regulation of CDCP1 in cancer cells *in vitro*, and significant tumor growth inhibition *in vivo* (38).

How does AHCC suppresses the expression of CDCP1? It is not yet clear which molecule, acting upstream of CDCP1, is down-regulated by AHCC. Chiu *et al*. reported that ADAM9 enhanced the expression of CDCP1 by suppressing miR-218 in lung cancer cells (39). In addition, Cao *et al*. reported that CDCP1 was regulated by HIF-2α at mRNA and protein levels in HCC cell lines (40). Unfortunately, we could not show down-regulation of ADAM9 or HIF-2α in cancer cells by *in vitro* treatment with AHCC (data not shown).

Although the mechanism that mediates down-regulation of CDCP1 by AHCC is not clear, AHCC is suggested as a possible candidate for treating progressive pancreatic cancer.

Conflicts of Interest

The Authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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