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COMMUNICATION

Serum Autotaxin is not a Useful Biomarker for Ovarian Cancer

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Abstract Autotaxin (ATX) is a glycoprotein that was first identified in the conditioned medium of human melanoma cells as an autocrine motility factor. It possesses lysophospholipase D activity, producing the bioactive lipid mediator lysophosphatidic acid (LPA) from lysophosphatidylcholine. Enhanced expression of ATX mRNA has been reported in various cancer cells and tissues, and it has been speculated that ATX overexpression in cancer cells may be associated with aberrant LPA production. LPA and ATX have been implicated in cancer progression and metastasis, and ovarian cancer is a representative example. In the present study, we measured the serum ATX antigen levels in patients with ovarian cancer and evaluated the usefulness of this parameter for clinical laboratory testing. The serum ATX antigen levels were not increased in ovarian cancer patients as compared with the levels in healthy subjects, and the serum ATX may not be useful as a biomarker for ovarian cancer.

Keywords Autotaxin · Clinical laboratory testing · Immunoenzymetric assay · Lysophosphatidic acids · Ovarian cancer · Tumor marker

Abbreviations

LPA	Lysophosphatidic acid
ATX	Autotaxin
LysoPLD	Lysophospholipase D
CA125	Cancer antigen 125

Introduction

Lysophosphatidic acid (1- or 2-acyl-*sn*-glycero-3-phosphatidic acid, LPA) is a simple lysophospholipid, and is attracting great attention as a lysophospholipid mediator. This bioactive lipid exerts important biological actions, including cell proliferation, migration and survival [1]. The multiple actions of LPA are explained by its binding to and activation of specific G-protein-coupled receptors (LPA1-6), leading to subsequent stimulation of the small GTPases, Ras, Rho and Rac [1–3].

The precise mechanism underlying the extracellular production of LPA has been elucidated in recent studies. In the plasma, autotaxin (ATX) plays a pivotal role in the production of LPA [1, 4]. ATX is a glycoprotein which was

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first discovered in the conditioned medium of human A2058 melanoma cells as an autocrine motility factor [1]. Later, it was revealed that ATX possesses lysophospholipase D (lysoPLD) activity, which hydrolyzes lysophosphatidylcholine to produce LPA [4].

LPA has been shown to be involved in several cellular processes such as proliferation, progression and invasion in in-vitro studies [1, 5–7]. On the other hand, enhanced expression of ATX mRNA has also been reported in various metastatic cancer cells and tissues [1, 7–10], and it has been speculated that ATX overexpression in cancer cells may be associated with aberrant LPA production. Together with these findings, not only LPA, but also ATX are likely to play critical roles in the pathophysiology of cancers.

Several studies have indicated that ATX and LPA are also related to the development/progression of ovarian cancer. For example, LPA and ATX have been demonstrated to promote ovarian cancer progression and invasion [6, 7]. ATX has been shown to delay apoptosis induced by carboplatin in ovarian cancer cells [8]. In addition, ATX and LPA receptors have been shown to be expressed in these cells [7, 8]. These studies clearly suggest that ATX and LPA are involved in the onset/progression of ovarian cancer.

Previous studies have investigated whether LPA can serve as a potential biomarker for ovarian cancer. The plasma LPA levels have been found to be increased in patients with ovarian cancer [11]. However, another group reported no difference in the plasma LPA levels between patients with ovarian cancer and healthy controls [12]. At present, whether plasma LPA might serve as a useful marker of ovarian cancer is still controversial. One of the reasons for this discrepancy is the difficulty in plasma LPA measurement. We previously reported that measurement of the plasma LPA concentration for clinical purposes has the critical and difficult problem; plasma levels of LPA can be easily altered during the sample preparation and preservation [13]. Therefore, re-examination conducted under stringent conditions to minimize any increase of the LPA level after sampling is needed for evaluation of the usefulness of plasma LPA measurement for ovarian cancer.

While plasma/serum LPA increases dramatically if samples are not handled properly, the serum ATX/lysoPLD remains relatively stable [13]. Serum ATX measurement seems to allow easier handling of the samples than plasma LPA measurement, and we confirmed that the ATX/lysoPLD antigen concentration and activity were well correlated with the plasma LPA concentration [10, 14–16]. Therefore, the plasma LPA can be estimated from the serum ATX. In the present study, we measured the serum ATX antigen levels in patients with ovarian cancer and evaluated the usefulness of this parameter for clinical laboratory testing.

Methods

The serum samples used in this study were residual samples of those obtained for laboratory analyses (for medical checkups). The study was conducted with the approval of the Institutional Research Ethics Committee of the Faculty of Medicine, the University of Tokyo. Informed consent from the patients was obtained for the use of the samples. Commercially available serum of ovarian cancer patients and healthy subjects were obtained from SLR Research Corporation (Carlsbad, CA, USA), BioTheme Research Solutions, Inc. (Davie, FL, USA) and ProMedDx, LLC (Norton, MA, USA).

The ATX antigen levels in the serum were determined by a two-site immunoenzymetric assay using the ATX assay reagent and the TOSOH AIA system (TOSOH, Tokyo, Japan) [14]. Serum cancer antigen 125 (CA125) levels were also analyzed by a two-site immunoenzymetric assay. The statistical significance of the differences between two groups was determined by an unpaired Student's t test. The correlations were evaluated by linear regression analysis. $p < 0.05$ was considered to be indicative of statistical significance.

Results

We first compared the ATX antigen concentrations in residual serum samples between ovarian cancer patients and healthy subjects (Table 1-A). No significant difference in the mean serum ATX level was observed between the patients and healthy subjects ($p = 0.946$). We then examined the correlation between the serum ATX and the serum CA125 in ovarian cancer patients. CA125 is believed to be the best biomarker for ovarian cancer, and is increased to above 35 U/mL in about 80 % of women with epithelial ovarian cancer [17]. No significant correlation was observed between ATX and CA125 ($p = 0.797$, Table 1-A). Similarly, no significant difference of the ATX level was observed between the patients and healthy subjects when commercially available sera were employed ($p = 0.110$, Table 1-B). Slight but significant correlation was detected between ATX and CA125 in commercially available serum ($r = 0.347$, $p < 0.001$) although its significance remains to be solved. When we analyzed the relationship between the serum ATX concentrations and the clinical course in two patients with ovarian cancer, no changes in the serum ATX were detected after chemotherapy, while the serum CA125 levels markedly decreased after chemotherapy (data not shown).

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