Clinical Rheumatology (2018) 37:1017–1024
https://doi.org/10.1007/s10067-018-4014-5

ORIGINAL ARTICLE

ADAM-17 is expressed in the inflammatory myopathy and is involved with interstitial lung disease

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Received: 29 October 2017 / Revised: 23 January 2018 / Accepted: 29 January 2018 / Published online: 6 February 2018

Abstract

The "A disintegrin and metalloprotease" (ADAM) family is thought to play an important role in tissue destruction and inflammatory reactions. ADAM-17 was first described as the protease responsible for tumor necrosis factor (TNF)-α shedding. Here, we have shown the expression of ADAM-17 in inflammatory myopathy and demonstrated the role of inflammation in interstitial lung diseases (ILD). ADAM-17 in inflammatory myopathy serum [polymyositis ($n = 26$), dermatomyositis ($n = 34$), and clinically amyopathic dermatomyositis ($n = 10$)] and healthy control ($n = 19$) was measured using enzyme-linked immunosorbent assay. The relationship between ADAM-17 and clinical data was examined. Finally, we performed immunohistological analysis to investigate the expression of ADAM-17 on the muscles of the inflammatory myopathy patients. ADAM-17 in inflammatory myopathy was significantly higher than that in healthy control (mean ± SEM, 1048 ± 312 and 36 ± 18 pg/ml, respectively; $p < 0.05$). ADAM-17 in post-treatment with corticosteroid and/or immunosuppressant serum was significantly decreased compared with that in pre-treatment serum (1465 ± 562 and 1059 ± 503 pg/ml, respectively; $p < 0.01$). ADAM-17 was significantly positively correlated with fractalkine/CX3CL1 and CXCL16. In addition, ADAM-17 in inflammatory myopathy with ILD patients ($n = 46$) was significantly higher than that in non-ILD patients ($n = 24$) (1379 ± 454 and 413 ± 226 pg/ml, respectively; $p < 0.05$). We found the expression of ADAM-17 on muscle biopsy tissue. ADAM-17 is expressed in inflammatory myopathies especially ILD, suggesting that ADAM-17 plays a role in lung fibrosis. ADAM-17 may be a potential target in inflammatory myopathies with ILD.

Keywords ADAM-17 · CXCL16 · Fractalkine/CX3CL1 · Inflammatory myopathy · Interstitial lung disease

Introduction

Polymyositis and dermatomyositis (PM/DM) are forms of idiopathic inflammatory myositis [1]. DM is identified by characteristic skin manifestations and muscular weakness [2]. However, PM is defined as subacute myopathy without the skin rash seen in DM [3]. In addition, amyopathic DM (ADM) is clinically diagnosed in a patient who has the typical DM skin rash but no or little muscular weakness [4]. PM/DM is occasionally complicated by interstitial lung disease (ILD) [5]. ILD in PM/DM is a major cause of rapid death from these diseases [6]. Several studies have shown that rapidly progressive ILD with a poor prognosis occurs in patients with ADM [7]. These patients are often resistant to intensive therapy including high-dose corticosteroids and immunosuppressive agents, resulting in fetal respiratory failure [8]. Rapidly progressive ILD in ADM has been reported predominantly in Asia [9].

The "A disintegrin and metalloprotease" (ADAM) family is thought to play an important role in tissue destruction and inflammatory reaction in vivo [10]. ADAMs are also involved in the amputation from the cell surface of inflammatory cytokines [11].

ADAM-17 was first described as the protease responsible for tumor necrosis factor (TNF)-α shedding [12]. In addition, ADAM-17 is involved in the physiological cleavage of membrane-anchored cytokines and cytokine receptors, such

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as fractalkine/CX3CL1 and interleukine (IL)-6 receptor, releasing them in soluble form [13].

The implication of ADAM-17 substrates in immunoregulation has made this enzyme an efficient therapeutic target in the treatment of several pathological conditions including airway inflammation and arthritis [14, 15]. Hence, ADAM-17 is expressed in synovial tissue, primarily in macrophage and fibroblast-like synovial cells, and cartilage in patients with rheumatoid arthritis (RA) [12]. Abnormal ADAM-17 activity and expression may contribute to the development of several pathological conditions, including RA [16].

Fractalkine/CX3CL1 is expressed in affected muscle in a murine model of experimental autoimmune myositis (EAM) and CX3CR1 is expressed on infiltrated CD4+ and CD8+ T cells and macrophages in muscle [17]. Moreover, the serum level of soluble CX3CL1 is elevated in patients with PM and DM, and is correlated with disease activity [17].

However, the function of ADAM-17 in myositis is unclear. Here, we have shown the expression of ADAM-17 in inflammatory myopathy, especially the relationship between ADAM-17 and ILD.

Materials and methods

Patients

We used data from a cohort of PM, DM, and CADM patients (2003–2015), who were diagnosed by the criteria developed by Bohan and Peter. DM is identified by characteristic skin manifestations such as Gottoron's papules or heliotrope rash, muscular weakness, the elevation of serum creatine kinase (CK) levels, the electromyogram, and the muscle tissue. PM is defined as subacute myopathy without the skin rash seen in DM. The sera were collected from the patients before and after the initial treatment.

ILD was diagnosed by clinical findings as follows: exertional dyspnea, nonproductive cough, fine crackles, and reticular shadow on chest radiographs or ground-glass opacity on chest high-resolution computed tomography.

In general, clinically amyopathic dermatomyositis (CADM) is the combination of amyopathic dermatomyositis (ADM) and hypomyopathic dermatomyositis (HDM). CADM is characterized by Gottoron's papules or heliotrope rash with no symptoms or sign of muscles weakness, and normal serum creatine kinase (CK) levels [18]. The pathological findings are normal or with scant lymphocyte infiltration with normal muscle structure [19].

The disease activity was defined as myalgia, active skin disease, symmetrical and proximal muscle weakness with serum CK elevation, or gradual or rapidly progressive ILD accompanied by the findings described above. We obtained written informed consent from all patients who enrolled in the study. The study received approval from the Bio-Ethics Committee of the Department of Medicine, Showa University School of Medicine (No. 1892).

Enzyme-linked immunosorbent assay

ADAM-17, fractalkine/CX3CL1, and CXCL16 in serum from patients with inflammatory myositis at pre- and post-treatment with immunosuppressants were measured using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN) following the manufacturer's protocol. Briefly, 96-well plates were coated with mouse anti-human antibody as the primary antibody, and serum or recombinant ADAM-17, fractalkine/CX3CL1, or CXCL16 was added. The plates were then washed, and biotinylated goat anti-mouse antibody was added, followed by streptavidin-horseradish peroxidase. The plates were developed using tetramethylbenzidine substrate (TMB; Sigma-Aldrich, ST. Louis, MO) and were read on a microplate reader. The concentration in each sample was measured at 450 nm.

Cell culture

Human lung fibroblasts (HLFs) were purchased from the American Type Culture Collection (Manassas, VA). HLF was cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum. HLFs were seeded at 1×10^5/ml in a six-well plate and were stimulated with 20 ng/ml TNF-α or 100 ng/ml IL-6 + 100 ng/ml IL-6 receptor (IL-6R) at 24 h. Conditioned medium were collected, and ADAM-17 was measured using ELISA.

Immunohistochemistry

Muscle specimens were obtained by muscle biopsy. The specimens were frozen immediately in chilled isopentane precooled in liquid nitrogen, and then, cryostat sections 10 μm thick were prepared. To analyze ADAM-17 expression, after fixing in cold acetone, the sections were treated with 3% H_2O_2 in phosphate-buffered saline (PBS) for 5 min, and then with 5% goat serum and 20% fetal bovine serum (FBS) in PBS for 1 h. The sections were incubated with 10 μg/ml rabbit anti-human ADAM-17 antibody (Abcam, Cambridge, MA) or rabbit IgG as a control. Biotinylated goat anti-rabbit IgG (Vector Laboratories, Burlingame, CA) was used as the secondary antibody. Vectastain ABC HRP reagent (Vector Laboratories) was then added. DAB peroxidase (HRP) was used. The sections were counterstained with hematoxylin. To determine the expression of ADAM-17 in lung fibroblast, immunohistrogical staining was demonstrated. Briefly, cultured HLF was fixed with cold acetone. Rabbit anti-human ADAM-17 (Abcam) was used as primary antibody.

Statistical analysis

The data were analyzed using the Mann-Whitney *U* test and Student's *t* test assuming equal variances. The relationship between ADAM-17 and fractalkine/CX3CL1 or CXCL16 in the serum from inflammatory myositis patients was evaluated using Spearman's rank correlation. The data are reported as the means ± SEM. *p* values less than 0.05 were considered significant.

Results

ADAM-17 expression on inflammatory myopathy tissues

First, we performed immunohistological analysis to examine the expression of ADAM-17 in muscles of inflammatory myopathy patients before treatment. We found the expression of ADAM-17 in muscle biopsy tissue of PM with ILD (Fig. 1a, b).

Clinical characteristics of study subjects

The patient characteristics are summarized in Tables 1 and 2. Table 1 shows the characteristics of the patients in this study. Twenty-six patients were diagnosed with PM, 34 patients were diagnosed with DM, and 10 patients were diagnosed with CADM. Forty six of 70 patients (66%) were complicated with ILD. Seventeen patients were treated with only corticosteroids, and 53 patients were treated with corticosteroids and immunosuppressants and/or immunoglobulin. Despite of intensive treatment, six patients died.

Table 2 shows the characteristics of the patients with or without ILD. Forty six of 70 patients (66%) were complicated with ILD [PM ($n = 16$), DM ($n = 20$), and CADM ($n = 10$)]. CK and lactate dehydrogenase (LDH) in the serum of the patients with ILD were significantly higher than those in the serum of the patients without ILD. All anti-Jo-1 antibody-positive patients were complicated with ILD.

Expression of ADAM-17 in inflammatory myopathy serum

ADAM-17 in inflammatory myopathy was significantly higher than that in healthy controls ($n = 19$) (mean ± SEM, 1048 ± 312 and 36 ± 18 pg/ml, respectively; $p < 0.05$; Fig. 2a). To determine the differences in diseases, we showed ADAM-17 in PM, DM, and CADM. ADAM-17 was not different between PM, DM, and CADM (Fig. 2b). ADAM-17 was not different between anti-Jo-1 antibody-positive and anti-Jo-1 antibody-negative in ILD patients (Fig. 2c). After finding that ADAM-17 was present in serum inflammatory myopathy, we wondered whether the level of ADAM-17 was decreased after treatment. ADAM-17 in corticosteroid- and/or immunosuppressant-treated patient serum was also significantly decreased compared with that in pre-treated patient serum (1465 ± 562 and 1059 ± 503 pg/ml, respectively; $p < 0.01$; Fig. 2d). In order to determine whether ADAM-17 is involved in muscle disorder or lung disorder, we performed

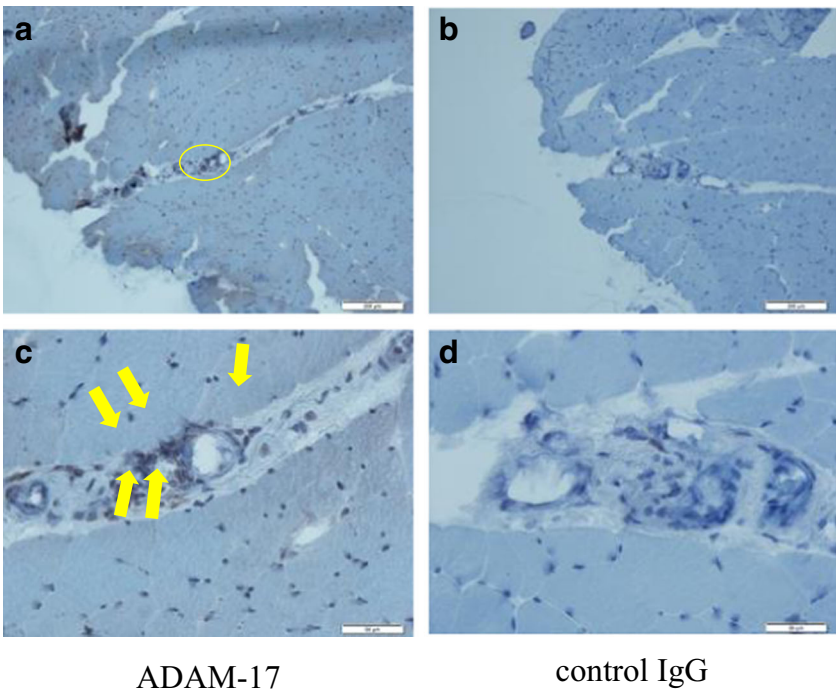

Fig. 1 ADAM-17 is expressed on the muscle tissue of an inflammatory myopathy patient. **a**–**d** Representative photomicrographs of muscle tissue samples from patients with inflammatory myopathy. **a** and **b** Cryosections were stained for ADAM-17. ADAM-17 expression on inflammatory cells (circle and arrow). **a** Original magnification, × 100. **b** Original magnification, × 400. **c** and **d** Cryosections were stained for control IgG. **c** Original magnification, × 100. **d** Original magnification, × 400

Table 1 Characteristics of the patients in this study

	PM	DM	CADM	Total
Number	26	34	10	70
Number of female (%)	17 (65)	22 (65)	6 (60)	45 (64)
Age	57.2 ± 3.3	58.9 ± 2.8	53.8 ± 3.7	57.5 ± 1.9
Number of case of new onset	25	29	10	64
Serum creatine kinase (IU/l)	2864.6 ± 648.8	2603.9 ± 508.2	126.1 ± 35.6	2346.8 ± 358.9
ILD (%)	16 (62)	20 (59)	10 (100)	46 (66)
Anti-Jo-1 antibody-positive (%)	4 (15)	3 (9)	1 (10)	8 (11)

the relationship between ADAM-17 and clinical data. First, we analyzed data between KL-6 and ADAM-17. KL-6 was positively correlated with ADAM-17 (Fig. 3a). On the other hand, there was no correlation between CK and ADAM-17 (Fig. 3b). There was no correlation between ADAM-17 and delta KL-6 or CK.

Fractalkine/CX3CL1 was overexpressed in inflammatory myopathy and was correlated with disease activity [17]. Fractalkine/CX3CL1 was one of the inflammatory cytokines which was cleaved by ADAM-17. ADAM-17 was significantly positively correlated with fractalkine/CX3CL1 (Fig. 4a). Moreover, fractalkine/CX3CL1 was reported to be contributed to the inflammatory cell infiltration into the affected muscle and lung in inflammatory myopathy patients [17]. CXCL16 was also reported as inflammatory cytokine, which was cleaved by ADAM-17. ADAM-17 was significantly positively correlated with CXCL16 (Fig. 4b).

In addition, we previously explained that there was a relationship between ADAM-17 and ILD. ADAM-17 in inflammatory myopathy with ILD patients ($n = 46$) was significantly higher than that in non-ILD patients ($n = 24$) (1379 ± 454 and 413 ± 226 pg/ml, respectively; $p < 0.05$; Fig. 5a), while ADAM-15 showed no difference between the ILD and non-ILD groups. To examine the characteristics of ADAM-17-positive or ADAM-17-negative patients, ADAM-17-negative group was defined as serum under 400 pg/ml. KL-6 in ADAM-17-positive ILD patients was significantly higher than that in ADAM-17-negative ILD patients (Fig. 5b). The age or CK was not different between ADAM-17-positive and ADAM-17-negative in ILD patients. 57.8% of the patients who were anti-Jo-1 antibody-negative have ILD. 57.5% of the patients who were ADAM-17-negative have ILD. Finally, in order to determine the expression of ADAM-17 in lung tissues, immunohistochemistry was performed. We found ADAM-17 was expressed in HLF (Fig. 5c, d).

In summary, we showed the expression ADAM-17 on inflammatory myopathy tissue, serum, and HLF.

Discussion

ADAM-17 has been found as a metalloproteinase that cleaves cytokines and chemokines such as TNF-α, interleukine-6 receptor (IL-6R), and fraktalkine/CX3CL1. TNF-α or IL-6 is involved in rheumatoid arthritis (RA) pathogenesis, and anti-TNF-α or anti-IL-6 is developed to treat RA. Regarding autoimmune diseases, ADAM-17 in RA is examined. Ohta et al. reported that expression of ADAM-17 at protein level in RA synovial tissue (ST) was significantly stronger than that in osteoarthritis (OA) [20]. Margherita et al. also showed that Furin, ADAM-17, TNF-α, and tumor-necrosis-factor-converting-enzyme (TACE)-TNF-α-Amphiregulin (AREG) proteins, detected in acinar and ductal cells of human salivary glands from Sjogren's syndrome patients, increased remarkably in comparison with biopsies of labial salivary grands

Table 2 Characteristics of patients with or without ILD

	ILD	Non-ILD	*p* value
Number	46	24	
Age	57.5 ± 2.1	57.6 ± 3.7	0.665
Number of females (%)	35 (76)	10 (42)	
PM/DM/CADM	16/20/10	10/14/0	
Lactate dehydrogenase (U/l)	529.1 ± 52.2	570.8 ± 75.6	0.553
Serum creatine kinase (IU/l)	1718.6 ± 319.5	3550.7 ± 805.2	0.039
KL-6 (U/ml)	790.8 ± 99.6	568.1 ± 207.1	0.006
Anti-Jo-1 antibody-positive	8	0	

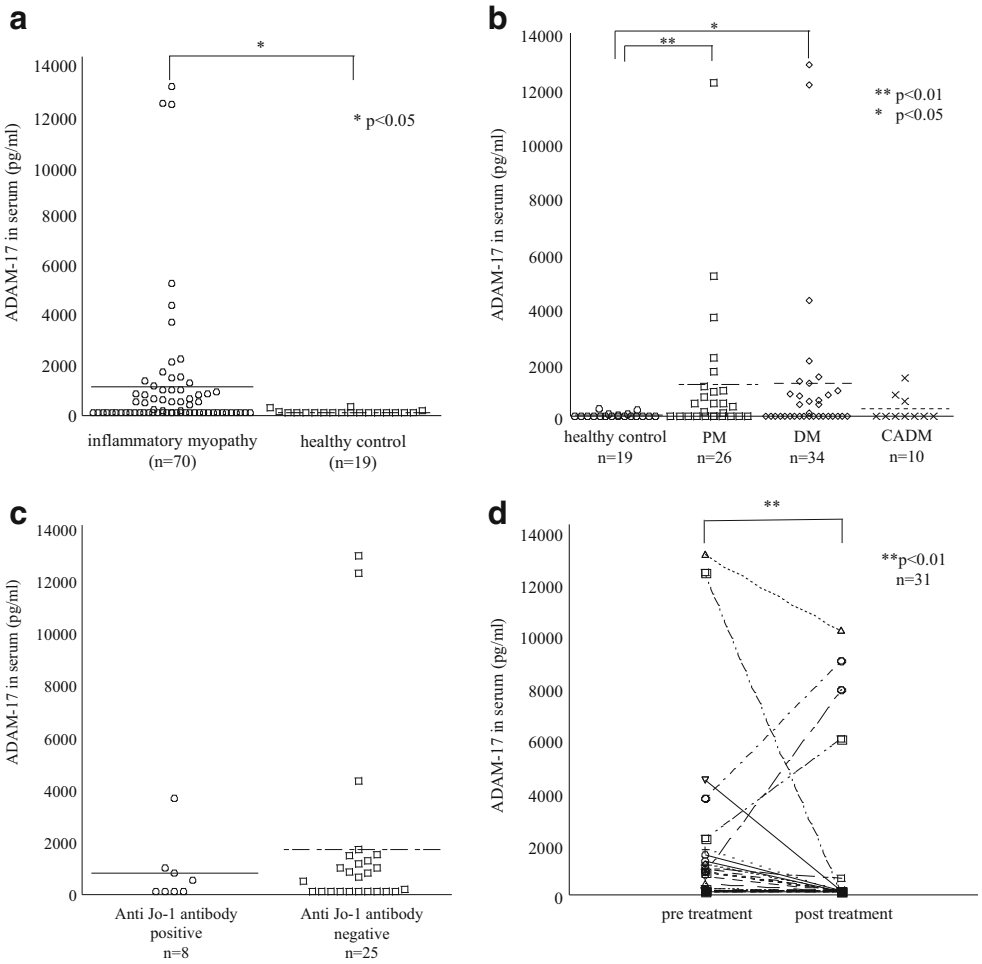

Fig. 2 ADAM-17 is expressed in the serum of inflammatory myositis patients. **a** The level of ADAM-17 in the sera of inflammatory myositis patients was significantly higher than that in healthy control sera. **b** The level of ADAM-17 was not different between PM, DM, and CADM. **c** The level of ADAM-17 was not different between anti-Jo-1 antibody-positive and anti-Jo-1 antibody-negative in ILD patients. **d** The level of ADAM-17 in the sera of inflammatory myositis patients was decreased after treatment with steroid and/or immunosuppressants (n = number of patients, p value is less than 0.05)

from health controls [21]. In this study, we first found that ADAM-17 was expressed on inflammatory myositis tissues.

Next, we focused on ADAM-17 expression in inflammatory myopathy serum. We found that ADAM-17 in inflammatory myopathy was significantly higher compared with that in healthy control. We previously reported that ADAM-17 level was markedly higher in RA patients than in healthy individuals [16]. As for cytokine expression, Lundberg et al. reported that cytokine expression in muscle tissue of patients with inflammatory myopathy is dominated by IL-1α, IL-1β, and transforming growth factor (TGF) β-3 [22]. We found that the level of ADAM-17 was decreased after treatment. These

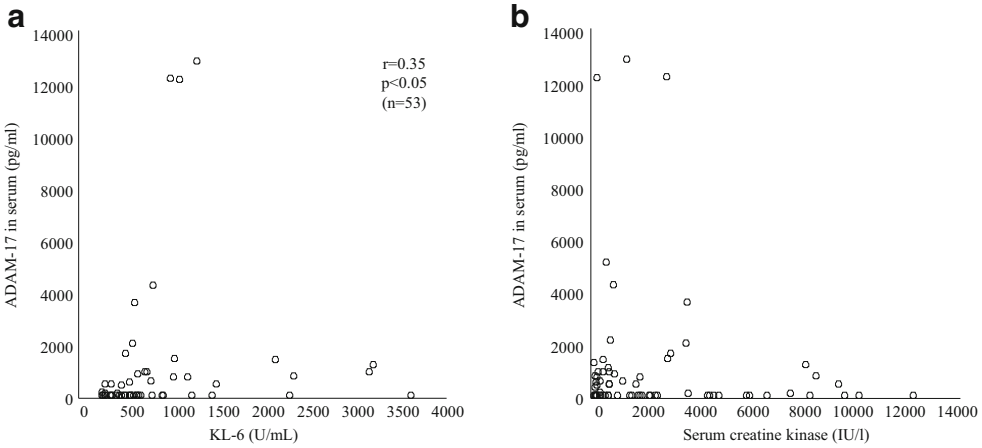

Fig. 3 Relationship between ADAM-17 and clinical data. **a** The level of KL-6 in the sera of inflammatory myositis patients was positive correlated with ADAM-17. **b** The level of CK in the sera of inflammatory myositis patients was not correlated with ADAM-17 (n = number of patients, p value is less than 0.05)

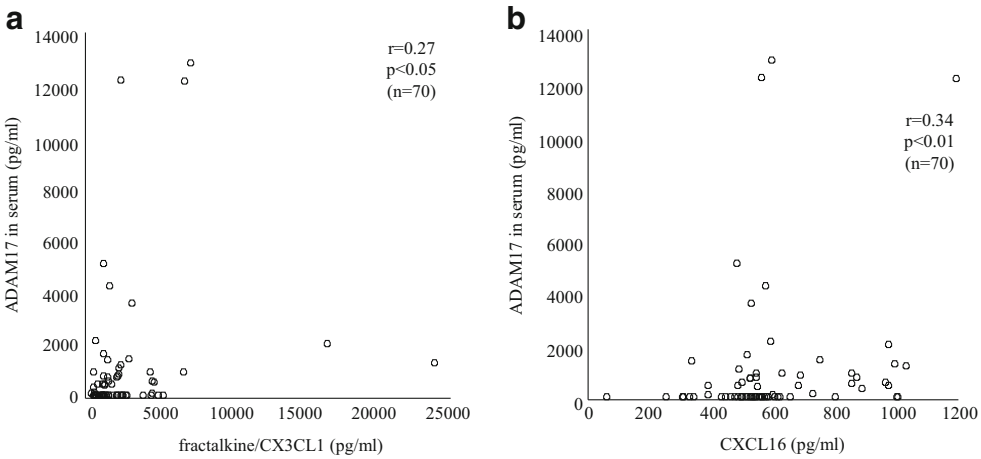

Fig. 4 **a** The level of ADAM-17 in the sera of inflammatory myositis patients showed a significantly positive correlation with fractalkine/CX3CL1. **b** The level of ADAM-17 in the sera of inflammatory myositis patients showed a significantly positive correlation with CXCL16. (*n* = number of patients, *p* value is less than 0.05)

results suggesting that the expression of ADAM-17 are related to the activity of inflammatory myopathy.

Boel De Paepe et al. reported that TNF-α, mostly produced by helper T cells, provokes muscle fiber atrophy and stimulated major histocompatibility complex I (MHC-I) and expression of adhesion molecules. Suzuki et al. reported that fraktalkine/CX3CL1 in treatment patient serum was significantly decreased compared with that in pre-treatment patient serum [17]. We clarified that ADAM-17 was correlated with fractalkine/CX3CL1, investigating that ADAM-17 was related via secretion of the cytokines and chemokines in the inflammatory myopathy.

Interestingly, Suzuki et al. also showed the interaction between fractalkine/CX3CL1 and CX3CR1 might contribute to

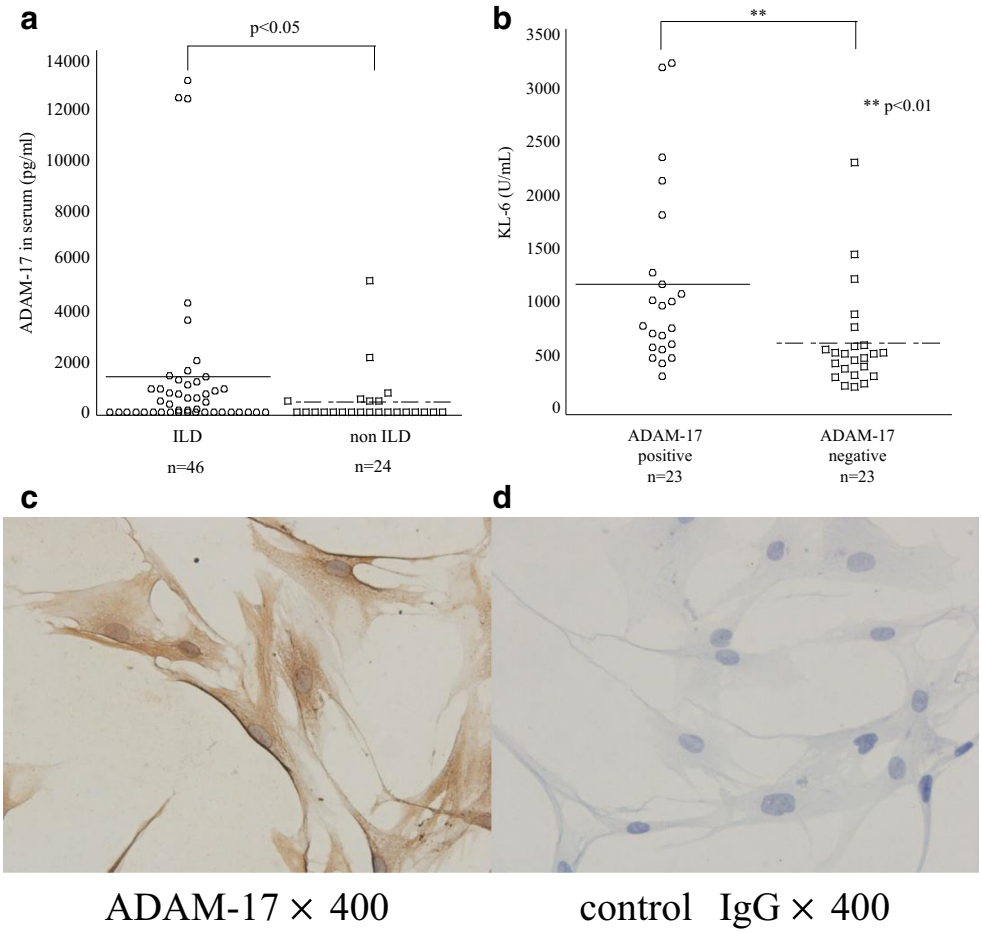

Fig. 5 **a** ADAM-17 in the sera of inflammatory myopathy patients with ILD is significantly higher than that in the sera of inflammatory myopathy without ILD. **b** The level of KL-6 in the sera of ADAM-17-positive ILD patients was significantly higher than that in the sera of ADAM-17-negative ILD patients (*n* = number of patients, *p* value is less than 0.05). **c** and **d** ADAM-17 was expressed in HLF. Representative photomicrographs of HLF. **c** HLF was stained for ADAM-17. ADAM-17 expression on HLF. Original magnification, × 400. **d** HLF was stained for control IgG. Original magnification, × 400

the inflammatory cell infiltration into affected muscle and lung with ILD in PM patients and DM patients [17]. Gono et al. demonstrated that IL-6, IL-8, TNF-α, and interferon gamma-induced protein-10 (IP-10)/CXCL10 are associated with global disease activity in PM/DM and these cytokine levels were high especially in the ILD subset [23]. We showed that ADAM-17 in inflammatory myopathy with ILD patients was significantly higher compared with that in non-ILD patients. Our findings support their reports. Taken together, these results clarify that ADAM-17 is associated with ILD.

In summary, we found the expression of ADAM-17 in muscle biopsy tissue. ADAM-17 in inflammatory myopathy was significantly higher than that in healthy controls. ADAM-17 was decreased after treatment with corticosteroids and/or immunosuppressants. ADAM-17 in ILD was significantly higher than that in non-ILD, suggesting that ADAM-17 might be a target for the treatment of inflammatory myopathy with ILD.

Acknowledgements We thank Ms. Takeuchi for performing all ELISAs.

Authors' contributions AN performed all assays with assistance from TI, SN, SI, TT, HF, and KW. TI also assisted with the acquisition of data. AN performed the statistical analysis. TI, KW, and TK conceived the study and participated in its design and coordination. TI assisted AN with drafting the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

We obtained written informed consent from all patients who enrolled in the study. The study received approval from the Bio-Ethics Committee of the Department of Medicine, Showa University School of Medicine (No. 1892).

Disclosures None.

Abbreviations ILD, interstitial lung disease; ADAM, A disintegrin and metalloprotease; TNF, tumor necrosis factor; PM, polymyositis; DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis; ADM, amyopathic DM; EAM, experimental autoimmune myositis; HDM, hypomyopathic dermatomyositis; CK, creatine kinase; ELISA, enzyme-linked immunosorbent assay; LDH, lactate dehydrogenase; FBS, fetal bovine serum; PBS, phosphate buffered saline; HLF, human lung fibroblasts; IL-6R, interleukine-6 receptor; RA, rheumatoid arthritis; ST, synovial tissue; OA, osteoarthritis; TACE, tumor-necrosis-factor-converting-enzyme; AREG, amphiregulin; TGF, transforming growth factor; MHC-I, major histocompatibility complex I; IP-10/CXCL10, interferon gamma-induced protein-10/CXCL10

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