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Autoantibodies to transcription intermediary factor (TIF)1 β associated with dermatomyositis

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Abstract

Introduction: Myositis specific autoantibodies are associated with unique clinical subsets and are useful biomarkers in polymyositis/dermatomyositis (PM/DM). A 120 kD protein recognized by certain patients with DM was identified and clinical features of patients with this specificity were characterized.

Methods: The 120 kD protein recognized by a prototype serum was purified and identified by mass spectrometry and immunological methods. Autoantibody to this 120 kD protein was screened in sera from 2,356 patients with various diagnoses from four countries, including 254 PM/DM, by immunoprecipitation of ³⁵S-methionine labeled K562 cell extracts. Clinical information of patients with this specificity was collected.

Results: The 120 kD protein, which exactly comigrated with PL-12, was identified as transcription intermediary factor TIF1 β (TRIM28) by mass spectrometry and validated by immunoassays. By immunofluorescence, anti-TIF1 β positivity showed a fine-speckled nuclear staining pattern. Four cases of anti-TIF1 β were identified; all are women, one each in a Japanese, African American, Caucasian, and Mexican individual. Three had a diagnosis of DM and one case was classified as having an undifferentiated connective tissue disease with an elevated CPK but without significant muscle symptoms. This individual also had a history of colon cancer, cervical squamous metaplasia and fibroid tumors of the uterus. Myopathy was mild in all cases and resolved without treatment in one case. The anti-TIF1 β specificity was not found in other conditions.

Conclusions: Anti-TIF1 β is a new DM autoantibody associated with a mild form of myopathy. Whether it has an association with malignancy, as in the case of anti-TIF1 γ , or other unique features will need to be evaluated in future studies.

Introduction

Autoantibodies to cellular constituents are clinically important biomarkers associated with particular diagnoses, specific clinical features or subsets of disease, helping to establish a diagnosis, and/or predicting organ involvement and prognosis [1,2]. In particular, in polymyositis/dermatomyositis (PM/DM) and scleroderma (systemic sclerosis, SSc) patients can be classified into several subsets associated with characteristic clinical features based on specific autoantibodies, since coexistence of other disease-specific autoantibodies is uncommon [3]. Each myositis specific

antibody (MSA) is associated with a unique clinical subset. For example, the anti-synthetase syndrome was named for the presence of anti-Jo-1 and other autoantibodies to aminoacyl tRNA synthetases found in a subset of patients with PM/DM whose clinical presentation was dominated by interstitial lung disease (ILD), Raynaud's phenomenon, arthritis, fever, and mechanic's hands [3,4]. Although new autoantibody specificities have been reported, approximately 40% to 50% of patients with PM/DM are still without a known MSA compared with only approximately 15% in SSc without association to known SSc antibodies [2]. Thus, identifying new MSA may help in monitoring PM/DM patients and several new clinically significant autoantibodies associated with DM including anti-p155/140 [5-11], anti-CADM (clinically amyopathic DM) 140/

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MDA5 (melanoma differentiation associated antigen 5) [10,12-14], anti-SAE (small ubiquitin-like molecule activating enzyme) and anti-MJ/NXP-2 have been reported recently [15,16]. Among these, anti-p155/140 has been studied extensively in a very short period of time due to its strong association with malignancy [5-9,11] which was confirmed by a recent meta-analysis [17]. However, this association does not appear to apply to children [7] or young adults [11]. p155 was identified as transcription intermediary factor1 γ , (TIF1 γ , also known as tripartite motif (TRIM) 33) [18]. A recent study in Japanese patients has identified the p140 as TIF1 α and another related molecule TIF1 β has also been identified as a target of autoantibodies in DM [11]. In the present study, we have independently identified the approximately 120 kD autoantigenic protein as TIF1 β by mass spectrometry. The presence of anti-TIF1 β and clinical features of American, Mexican, and Japanese patients with this specificity were characterized.

Materials and methods

Patients

A total of 2,356 sera, including 1,966 subjects enrolled in the University of Florida Center for Autoimmune Diseases (UFCAD) registry from 2000 to 2010, were studied. Diagnoses of the UFCAD patients include 434 systemic lupus erythematosus (SLE), 86 PM/DM (51 PM including 12 PM-SSc overlap, 35 DM), 121 SSc, and 122 rheumatoid arthritis (RA). Additionally, sera from 36 PM/DM (13 PM, 20 DM, 3 amyopathic DM) from St. Marianna University Hospital (Kawasaki, Japan), 74 PM/DM (18 PM, 56 DM) sera from Guadalajara and Mexico City (Mexico), 58 PM/DM (25 PM, 27 DM, 6 overlap: 4 PM-SSc, 1 DM-SLE, 1 PM-RA), 57 SSc, and 113 SLE, and 52 primary anti-phospholipid syndrome (PAPS) from Spedali Civili di Brescia (Brescia, Italy) were also screened. Diagnosis of PM/DM is by physician's assessment based on Bohan's criteria (PM/DM). Other diagnoses were established by the American College of Rheumatology (ACR) (SLE, SSc, RA) or European criteria (Sjögren's syndrome). Clinical information was from database and medical records. The protocol was approved by the Institutional Review Board (IRB). This study meets and is in compliance with all ethical standards in medicine, and informed consent was obtained from all patients according to the Declaration of Helsinki.

Materials and methods

Immunoprecipitation

Autoantibodies in sera were screened by immunoprecipitation using ³⁵S-methionine labeled K562 cell extracts [19]. Specificity of autoantibodies was determined using previously described reference sera. Analysis of RNA components of autoantigens was by urea-PAGE and silver

staining (Silver Stain Plus, Bio-Rad, Hercules, CA, USA) [20].

Identification of proteins by LC-MS/MS

The new unidentified autoantigen of 120 kD protein was purified using serum from the prototype patient. Immunoglobulin G (IgG) from 20 μ l of serum was crosslinked to protein A Sepharose beads using dimethylpiperimide. Protein was then affinity-purified from a cell extract of 4×10^8 K562 cells and fractionated by SDS-PAGE. The 120 kD protein band was cut following silver staining of the gel, trypsin-digested and analyzed by liquid chromatography - tandem mass spectrometry (LC-MS/MS) analysis on a hybrid quadrupole-TOF mass spectrometer (QSTAR elite, Applied Biosystems) at UF ICBR Protein Core. Tandem mass spectra were extracted by ABI Analyst version 2.0. All MS/MS samples were analyzed using Mascot (Matrix Science, London, UK; version 2.2.2). Scaffold (version Scaffold-02-03-01, Proteome Software Inc.) was used to validate MS/MS based peptide (> 95.0% probability) and protein identifications (> 99.0% probability and at least two identified unique peptides).

Affinity purification of the TIF1 β and western blot

Identity of the approximately 120 kD protein as TIF1 β was verified by immunoprecipitation followed by western blot (IP-WB) using an extract from 5×10^6 K562 cells and 2 μ l of human serum. Purified proteins were fractionated in 8% acrylamide SDS-PAGE, transferred to nitrocellulose filter and probed with mouse anti-TIF1 β monoclonal antibodies (mAb) (EMD Millipore, Billerica, MA, USA), followed by horseradish peroxidase-conjugated (HRP) goat anti-mouse Ig light-chain antibodies (Jackson ImmunoResearch Laboratories, Inc. West Grove, PA, USA) and developed with SuperSignal West Femto Chemiluminescent Substrate (Thermo Scientific, Rockford, IL, USA).

In another experiment, TIF1 β was affinity purified from an extract of 2×10^8 K562 cells using 10 μ g of anti-TIF1 β mAb, and purified proteins were fractionated by SDS-PAGE and transferred to nitrocellulose filter. Strips (2 mm width) of nitrocellulose filter were probed with mouse mAb and human autoimmune sera. Strips incubated with mouse mAb were then incubated with HRP goat anti-mouse Ig light-chain antibodies and developed, while samples probed with human sera were incubated with HRP-donkey IgG F(ab)'₂ anti-human IgG (γ -chain specific) antibodies (Jackson ImmunoResearch Laboratories, Inc.) and developed.

Immunofluorescent antinuclear antibodies

Immunofluorescent antinuclear/cytoplasmic antibodies (HEp-2 ANA slides; INOVA Diagnostics, San Diego, CA, USA) were tested using a 1:80-diluted human serum or 2 μ g/ml mouse mAb to TIF1 β . Secondary antibodies were DyLight 488 donkey IgG F(ab)'₂ anti-human or -mouse IgG (1:200 dilution, γ -chain-specific, Jackson ImmunoResearch Laboratories).

ELISA

Antigen-capture ELISA for anti-TIF1 β was performed using 2 μ g/ml mouse mAb to TIF1 β (Millipore), following a protocol that was used for other autoantibody systems [21]. Antibodies to TIF1 α (p140 of p155/140), TIF1 β , and TIF1 γ (p155) were also tested using full-length recombinant proteins from Abnova (TIF1 α and β , Taipei, Taiwan) and OriGene Technologies (TIF1 γ , Rockville, MD, USA), respectively. Wells of microtiter plates were coated using 0.5 μ g/ml of protein and ELISA was performed following standard protocol as described [22].

Results

First, the 120 kD protein was affinity purified using the human prototype serum and the identity of the protein was determined by LC-MS/MS. Sixteen unique (total of 18) peptides that contained sequences identical to TIF1 β were isolated as follows: aa128-136 DIVENYFMR ($n = 2$), aa254-261 KLLASLVK, aa283-290 QVSDVQKR, aa297-304 MAILQIMK, aa310-319 GRVLVNDAAQK, aa312-319 VLVNDAQK, aa312-327 VLVNDAQKVTEGQQR, aa331-337 QHWTMTK, aa408-427 IVAERPGTNSTG-PAPMAPPR, aa473-483 SGEGEVSGLMR ($n = 2$), aa493-507 LDLDLTADSQPPVFK, aa508-524 VFPGSTTEDYN-LIVIER, aa751-767 LSPPYSSPQEFAQDVGR, aa775-790 LTEDKADVQSIIGLQR, aa 780-790 ADVQSIIGLQR, and aa796-804 MNEAFGDTK. These peptides covered 19.5% (163/835 amino acids) of the sequence of TIF1 β . Since the reported molecular weight of TIF1 β is approximately 120 kD, it was considered a good candidate and its identity was validated using mAb to TIF1 β .

Immunoprecipitation

The 120 kD proteins immunoprecipitated by four sera (Figure 1A, lanes 1-4), both in size and appearance, appeared identical to the TIF1 β protein immunoprecipitated by the mAb, consistent with the identity of the 120 kD proteins as TIF1 β . TIF1 β showed a migration pattern similar to the known myositis autoantigen PL-12 but had a broader band in contrast to the sharp band of PL-12 (Figure 1A). Two sera (lanes 1-2) had strong reactivity, while the other two (lanes 3-4) were weak. When 20% of the sample of case two was run (lane 2), it showed an appearance that was very similar to the weak ones in lanes 3-4, suggesting that they are the same proteins. Although TIF1 β /TRIM28 and TIF1 γ /TRIM33 are in the same family of related proteins and their interactions have been reported [23], anti-TIF1 β mAb did not immunoprecipitate TIF1 γ /p155 (Figure 1A, lane TIF1 β mAb). Also, anti-TIF1 γ (p155/140) positive serum did not immunoprecipitate TIF1 β (Figure 1A, lane p155/140), consistent with a lack of crossreactivity and interactions between TIF1 β and TIF1 γ under the conditions used for immunoprecipitation. None of these four human sera with anti-TIF1 β antibodies

clearly immunoprecipitated TIF1 γ / α (p155/140) (Figure 1A). However, the serum from case three was positive for anti-TIF1 α by ELISA using recombinant protein (Table 1). Case four was negative for antibodies to recombinant TIF1 γ and α by ELISA. Also, none of the 23 anti-p155/140 positive sera in our cohort immunoprecipitated TIF1 β (data not shown). Case four had coexisting anti-Mi-2 antibodies (Figure 1A, lane Mi-2), cases two and four had anti-Su/Ago2, and case two also had anti-Ro and U1RNP. Sequential serum samples available for case two were tested by immunoprecipitation (Figure 1B). The levels of anti-U1RNP antibodies that were weakly positive at the initial visit increased followed by the development of additional autoantibodies to an unidentified protein of approximately 160 kD (white arrowhead).

Since many autoantigens in PM/DM are RNA-protein complexes, RNA components in immunoprecipitates were also analyzed by silver staining. No common RNA component was detected, suggesting TIF1 β is not complexed with specific RNA (data not shown).

Confirmation of the 120 kD protein as TIF1 β

The identity of the 120 kD protein immunoprecipitated by human sera as TIF1 β was confirmed by IP-WB (Figure 2A). The proteins immunoprecipitated by human autoimmune sera were recognized by mAb to TIF1 β , confirming the identity of the protein.

Antigen-capture ELISA using mouse anti TIF1 β mAb was also performed using serially diluted anti-TIF1 β positive sera (Figure 2B). All four anti-TIF1 β positive sera were positive in ELISA in titers up to 1:12,500 to 1:312,500. Control sera including anti-TIF1 γ or anti-Mi-2 positive sera and NHS, were all negative.

Western blot using affinity purified TIF1 β

Strips of nitrocellulose filter with TIF1 β affinity-purified by mAb were probed with mouse mAb anti-TIF1 β and human autoimmune sera. Mouse mAb strongly reacted with the purified TIF1 β protein; however, human autoimmune sera were negative when the western blot was developed using SuperSignal West Pico. Only the serum from case one was very weakly positive when developed using more sensitive SuperSignal West Femto (Figure 2C).

Immunofluorescence staining of anti-TIF1 β positive sera

HEp-2 ANA slides were stained with mouse anti-TIF1 β mAb or human sera (Figure 2D). Mouse mAb showed a fine nuclear speckled pattern sparing the nucleoli and without chromosomal staining (panel a). Relatively monospecific serum from a Japanese patient (case one) showed a pattern very similar to that of mAb (panel b). Other sera (cases two to four) also showed a fine speckled nuclear staining pattern (panels c-e); however, one serum (case three) also had large nuclear speckles (panel d). A serum

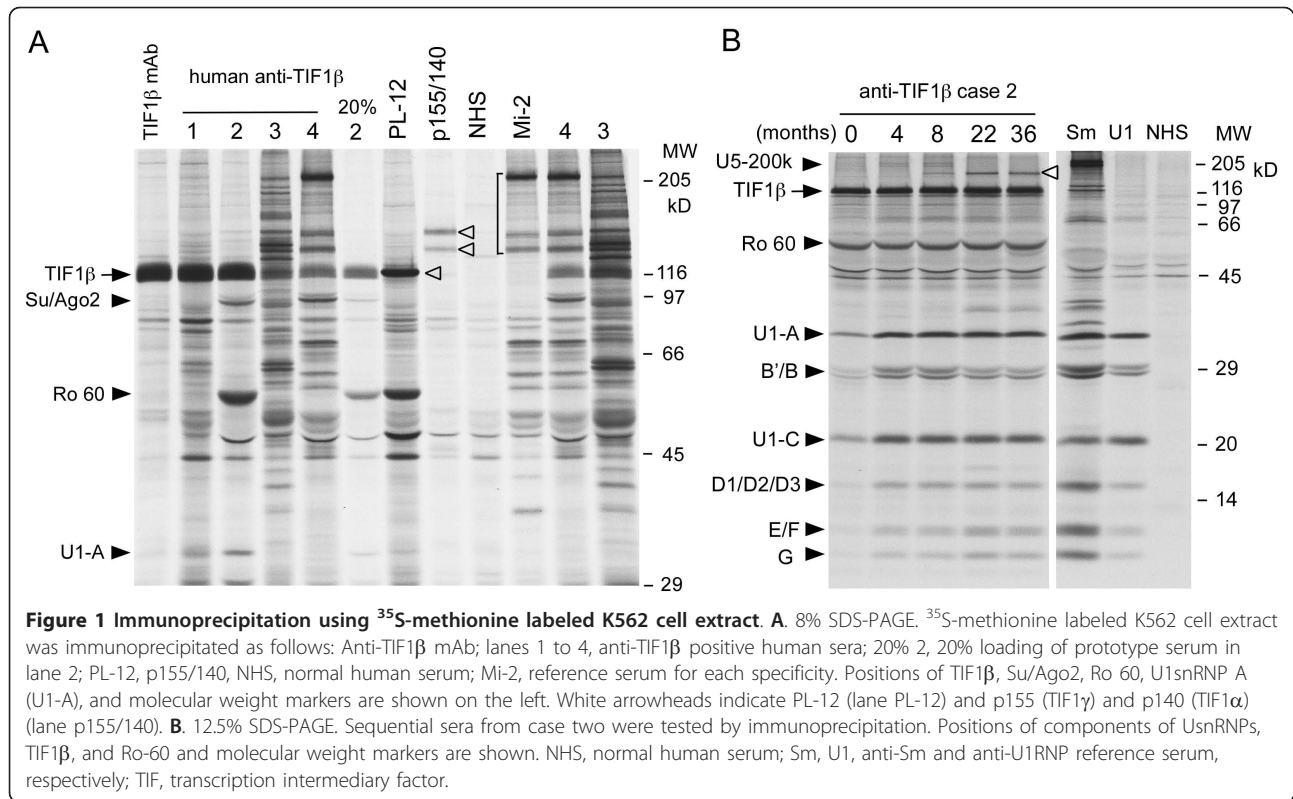
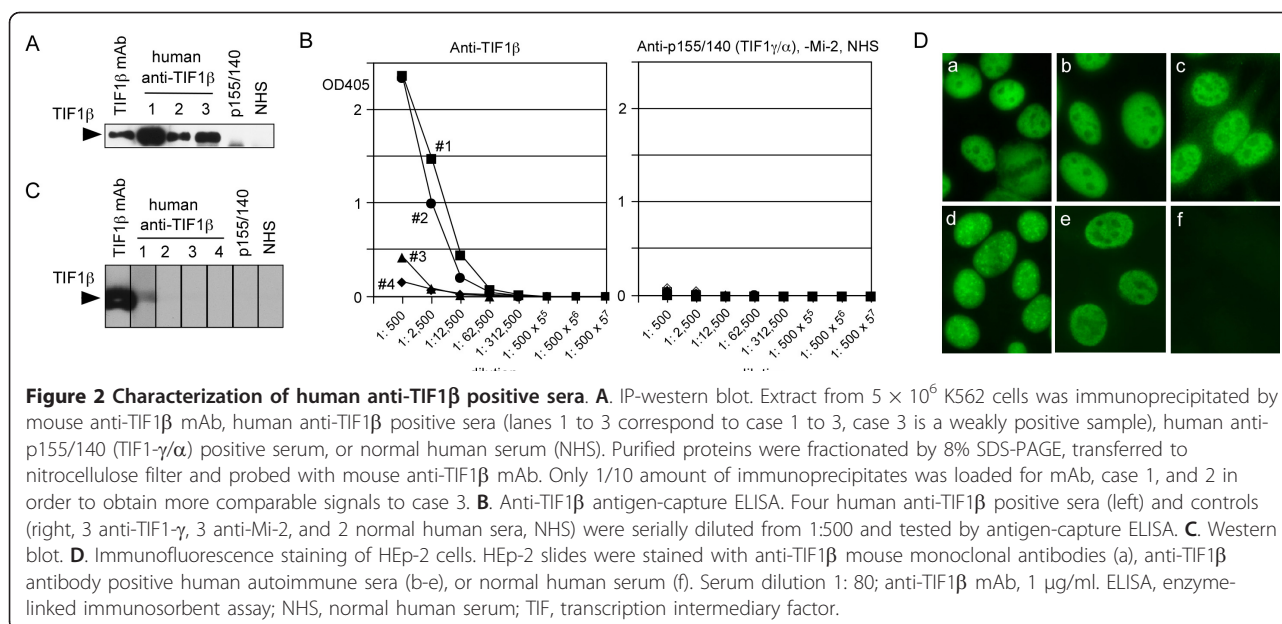


Table 1 Clinical features of patients with anti-TIF1β autoantibodies.

	1	2	3	4
Diagnosis	DM	UCTD	DM	DM
Symmetrical muscle weakness	P	N	P	Y
Muscle biopsy	Y	ND	ND	NA
Elevated muscle enzyme	Y	Y	Y	Y
EMG	myopathic pattern	myopathic pattern	myopathic pattern	NA
Dermatologic features	Y (G)	N	P (S)	Y (G, H, S)
Malignancy	N	Y	N	N
Interstitial lung disease	N	N	N	N
Dysphagia	Y	N	N	N
Raynaud's phenomenon	N	N	N	N
Arthritis	N	Y	N	N
CPK (U/L) initial	654	341	314	2414
/after Tx (lowest)	167	239		
Initial Tx	none	PSL 10 mg HCQ 200 mg NSAIDs	PSL 40 mg HCQ 200 mg	PSL 50 mg MTX 20 mg/w HCQ 150 mg
Response to Tx	NA	good	good	good
Other autoantibodies		Ro, Su, U1RNP (Sm)		Mi-2, Su
ELISA (RP) TIF1α	-	-	+	-
TIF1β	+	+	-	-
TIF1γ	-	-	-	-
antigen-capture ELISA				
TIF1α	-	-	-	-
TIF1β	+	+	weak +	weak +

DM, dermatomyositis; ELISA, enzyme-linked immunosorbent assay; EMG, electromyogram; G, Gottron; H, heliotrope; HCQ, hydroxychloroquine; MTX, methotrexate; N, no; NA, not available; ND, not done; NSAIDs, non-steroid anti-inflammatory drugs; P, possible; PSL, prednisolone; RP, recombinant protein; S, shawl sign; TIF, transcription intermediary factor; Tx, treatment; UCTD, undifferentiated connective tissue disease; Y, yes;



with coexisting anti-Mi-2 (case four) also had fine speckled nuclear staining (panel e).

Clinical manifestations of patients with anti-TIF1 β antibodies

Clinical features of anti-TIF1 β antibody positive cases are summarized in Table 1. All four were women, three with a diagnosis of DM and one classified as undifferentiated connective tissue disease (UCTD) with elevated creatine phosphokinase (CPK) but without significant muscle symptoms. Thus, anti-TIF1 β was found in 3/130 DM (1/35 Americans, 1/23 Japanese, 1/56 Mexicans) but 0/92 PM and none in SLE, SSc, or other conditions, suggesting that this specificity may be closely associated with DM, similar to antibodies to p155/140 (TIF1 γ/α). The Japanese DM patient (case one) had elevated CPK (654 IU/L), mild muscle weakness, myalgia, a positive muscle biopsy and electromyogram (EMG); however, her myopathy resolved without treatment. The UCTD case (case two) also had elevated muscle enzymes, but muscle symptoms were not clear. Moreover, she had leukopenia, lymphopenia and autoimmune hemolytic anemia. This case also had a history of colon cancer (at age 41), cervical squamous metaplasia and fibroid tumors of the uterus. Two American patients (cases two and three) had mildly elevated levels of CPK (approximately 300 IU/L) that were controlled with low to moderate doses of steroids. The Mexican case also had high CPK but responded well to initial treatment.

Discussion

In the present study, a 120 kD protein recognized by sera from four patients with DM or UCTD was identified as TIF1 β based on mass spectrometric analysis and

immunological confirmation, and it is closely related to a known cancer-associated DM autoantigen p155/140 (TIF1 γ/α). Since the mobility of TIF1 β in SDS-PAGE is identical to that of PL-12 (Figure 1), approximately 120 kD protein bands seen in IP will need to be cautiously interpreted. However, TIF1 β and PL-12 have distinctive immunofluorescence patterns, which should help to differentiate the specificities. Anti-TIF1 β produces a fine nuclear speckled pattern (Figure 2D) while anti-PL-12 gives a cytoplasmic pattern [24].

TIF1 α , TIF1 β , and TIF1 γ belong to the TIF family of transcription cofactors and are part of a tripartite motif superfamily (TRIM24, 28, and 33, respectively) [23]. TIF1 β /TRIM28, also known as Kruppel-associated box (KRAB)-associated protein 1 (KAP1), is a multi-functional protein involved in gene silencing, cell growth and differentiation, pluripotency, neoplastic transformation, apoptosis, DNA repair and the maintenance of genomic integrity [25]. A striking association of anti-p155/140 with cancer-associated DM has been described in several reports from the US [5], UK [7], Spain [9], Japan [6,8,10,11], and Korea [26] (reviewed in [9]), however, their association does not seem to apply to children [7] or young adults [11]. A Japanese PM/DM study that has just been published identified p140 as TIF1 α and confirmed the p155 as TIF1 γ [11]. In addition, seven cases with anti-TIF1 β , four with anti-TIF1 α and γ and two with anti-TIF1 γ have been reported. It should be noted that in contrast to a previous study limited to PM/DM [11], anti-TIF1 β antibodies were screened in 2,356 patients with various diagnoses in the present study, yet it was primarily associated with DM. Both studies suggest that anti-TIF1 β is much less prevalent than anti-p155/140. Six of their 77 anti-p155/140 positive

sera were also positive for anti-TIF1 β [11] whereas none of our 23 anti-p155/140 were anti-TIF1 β positive (data not shown). Although the difference observed between the two studies is not statistically significant, it is possible that coexisting patterns of autoantibodies to TIF family proteins are affected by genetic and/or environmental factors, selection bias (dermatology versus rheumatology clinic, for example) and other factors.

It has been shown that these TIF1 family proteins interact and work synergistically to suppress the development of malignancy in human and mouse models [23,27]. TIF1 β is overexpressed in various types of cancer tissues [28] and is associated with progression or metastasis of the cancer [29,30]. It would not be surprising if the production of anti-TIF1 β is also linked with cancer-associated DM as overexpression and modification of self-protein may trigger an autoimmune response. In the present study, one case with anti-TIF1 β had a history of colon cancer, squamous metaplasia in a cervical smear and fibroid tumors of the uterus, but malignancy was not recorded in the other three cases, possibly due in part to a short follow-up period. A recent study [11] showed two of seven cases with anti-TIF1 β had malignancy, possibly less frequently than anti-p155/140 positive cases.

In the case of the classic tumor suppressor gene p53, mutation and accumulation of p53 leads to the development of cancer as well as autoantibodies to p53, which is considered a result of broken immunological tolerance due in part to mutated p53 [31]. As TIF family proteins are known tumor suppressors [23,27] and are overexpressed in certain cancer tissues [28-30], a possible relationship between the development of autoantibodies to TIF and cancer may be explained by a similar mechanism. In this scenario, a mutation of TIF occurs as a primary event and triggers an autoimmune response against TIF, while cancer would develop due to the failed tumor suppressive activity of TIF. Further studies are necessary to determine whether anti-TIF1 β has a strong association with cancer similar to anti-TIF- γ and whether TIF mutations are the primary event.

Alternative or additional mechanisms of anti-TIF1 β production may be hypothesized based on the role of TIF1 β in viral infections. TIF1 β /KAP1 has been shown to play a critical role in controlling replication of Epstein-Barr virus [32], expression of murine endogenous retroviruses [33,34], latency regulation of Kaposi's sarcoma-associated herpesvirus (KSHV) [35], and replication of human papillomaviruses [36]. In this scenario, TIF1 β would interact with viral proteins and the putative viral-self protein complex may trigger autoantibodies to TIF1 β , similar to the induction of anti-p53 by a complex of viral simian virus 40 T protein and self p53 protein [37]. Association of virus and myositis autoantibody production has been suggested to occur by various pathways, including viral RNA

interaction with aminoacyl tRNA synthetase and molecular mimicry of viral protein and autoantigens [38,39]. More recently, a target antigen of anti-CADM140 was identified as an intracellular viral RNA receptor, melanoma differentiation-associated gene 5 (MDA5) [13]. Thus, any of these mechanisms may also be involved.

Conclusions

In summary, anti-TIF1 β has been characterized as autoantibodies associated with DM with a mild form of myopathy without lung involvement. TIF1 β is a multifunctional protein closely related to the known cancer-associated DM autoantigen p155/140 (TIF1 γ/α) involved in suppression of malignancy as well as viral replication [23,27]. Both mutation of TIF1 β and its interaction with viruses make an attractive hypothesis for the mechanism of production of autoantibodies to TIF1 β . Future studies should verify an association of anti-TIF1 β with malignancy and clarify mechanisms of its production.

Abbreviations

ACR: American College of Rheumatology; ANA: antinuclear antibody; CADM: clinically amyopathic dermatomyositis; CPK: creatine phosphokinase; DM: dermatomyositis; ELISA: enzyme-linked immunosorbent assay; EMG: electromyography; IgG: immunoglobulin G; IIF: indirect immunofluorescence; HRP: horseradish peroxidase; ILD: interstitial lung disease; IP: immunoprecipitation; IP-WB: immunoprecipitation followed by western blot; KAP1: Kruppel-associated box (KRAB)-associated protein 1; KSHV: Kaposi's sarcoma-associated herpesvirus; mAb: monoclonal antibody; MDA5: melanoma differentiation associated antigen 5; MSA: myositis-specific autoantibodies; OD: optical density; PAPS: primary anti-phospholipid syndrome; PM: polymyositis; RA: rheumatoid arthritis; SAE: small-ubiquitin-like modifier-1 activating enzyme; SD: standard deviation; SLE: systemic lupus erythematosus; SSC: scleroderma; TIF: transcription intermediary factor; TRIM: tripartite motif; UCTD: undifferentiated connective tissue disease.

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Authors' contributions

MS, JYFC, SJR, YL, and YY carried out the immunoassays. MS and EKLC designed the study. MS performed the statistical analysis. YY, HY, MVM, MP, LJJ, MAS, CCR, ESS, WHR, and AC enrolled patients for the study, collected information and maintained databases. MS, AC, and EKLC drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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