Systemic sclerosis, myositis and related syndromes - aetiology, pathogenesis and animal models

POS0603

AUTOANTIBODIES AGAINST A SUBUNIT OF MITOCHONDRIAL RESPIRATORY CHAIN COMPLEX I IN INCLUSION BODY MYOSITIS

Keywords: Autoantibodies, Myositis

A. Notarnicola[1,2], C. Hellstrom[3], B. Horuluoglu[1,2], C. Preger[1], F. Bonomi[4], B. De Paepe[5], J. De Bleecker[5], A. J. Van der Kooi[6], M. De Visser[6], S. Sacconi[7], P. Machado[8], U. A. Badrising[9], A. Rietveld[10], G. Pruijn[11], S. Rothwell[12], J. B. Lilleker[13,14], H. Chinoy[13,14,15], O. Benveniste[16], E. Svenungsson[1], H. Idborg[1,2], P. J. Jakobsson[1,2], P. Nilsson[3], I. E. Lundberg[1,2]. [1]*Karolinska Institutet and Karolinska University Hospital, Division of Rheumatology, Department of Medicine, Stockholm, Sweden*; [2]*Karolinska Institutet, Center for Molecular Medicine, Stockholm, Sweden*; [3]*KTH Royal Institute of Technology, Department of Protein Science, SciLifeLab, Stockholm, Sweden*; [4]*University of Florence-University Hospital Careggi, Dept Experimental and Clinical Medicine, Division of Rheumatology, Florence, Italy*; [5]*Ghent University Hospital, Department of Neurology and Neuromuscular Reference Center, Ghent, Belgium*; [6]*Amsterdam University Medical Centers, University of Amsterdam, Amsterdam Neuroscience, Department of Neurology, Amsterdam, Netherlands*; [7]*Nice University Hospital/ Institute of Research on Cancer and Aging of Nice, Research on Cancer and Aging, Nice, France*; [8]*University College London, Centre for Rheumatology & Department of Neuromuscular Diseases, London, United Kingdom*; [9]*Leiden University Medical Centre, Department of Neurology, Leiden, Netherlands*; [10]*Radboud University Medical Center, Department of Neurology, Center for Neuroscience Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands*; [11]*Radboud University, 11Department of Biomolecular Chemistry, Institute for Molecules and Materials, Nijmegen, Netherlands*; [12]*The University of Manchester, Division of Musculoskeletal & Dermatological Sciences, Manchester, United Kingdom*; [13]*The University of Manchester, Division of Musculoskeletal and Dermatological Sciences, Centre for Musculoskeletal Research, School of Biological Sciences, Manchester, United Kingdom*; [14]*Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Department of Rheumatology, Manchester, United Kingdom*; [15]*The University of Manchester, Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, Manchester, United Kingdom*; [16]*Pitié-Salpêtrière Hospital, Department of Internal Medicine and Clinical Immunology, Paris, France*

Background: Autoantibodies are found in up to 80% of patients with idiopathic inflammatory myopathies (IIM) and are associated with distinct clinical phenotypes [1]. Autoantibodies targeting cytosolic 5´-nucleotidase 1A (anti-cN1A) are currently the only known serum biomarker for the subgroup inclusion body myositis (IBM) (2), although detected even in other autoimmune diseases.
Objectives: To identify new autoimmune targets in IIM by antigen bead array assay.
Methods: In a first cross-sectional exploratory study, 357 antigens representing 268 proteins were incubated with plasma samples from 219 IIM (108 Polymyositis (PM), 80 Dermatomyositis (DM) and 31 IBM) patients, 349 Systemic Lupus Erythematosus (SLE) patients and 306 population controls for screening of IgG reactivity by antigen bead array. All samples were identified in the local biobank of the Rheumatology clinic, Karolinska University Hospital. Interesting results obtained for the IBM subgroup were then validated in an independent larger cohort of 287 patients with IBM followed at nine European rheumatological or neurological centers. IBM serum samples were explored by antigen bead array and results validated by western blot. As controls, serum samples from 30 patients with PM and 30 with DM, HLA-matched with the IBM Swedish cohort, were included. Demographics, laboratory, clinical, and muscle biopsy data of the IBM cohort was retrieved.
Results: In the exploratory study IgG reactivity towards NADH dehydrogenase 1 α subcomplex 11 (NDUFA11), a subunit of the membrane-bound mitochondrial respiratory chain complex I, was discovered with higher frequency in the IBM (9,7%) than PM (2,8%) and DM samples (2,5%), although the difference was not statistically significant. Anti-NDUFA11 IgG was also found in 2,3% of SLE and 2,6% of population control samples. In the validation study anti-NDUFA11 autoantibodies were detected in 11/287 IBM patients (3,8%), 0/30 PM and 0/30 DM patients. Reactivity against NDUFA11 could be confirmed by western blot (Table 1, Figure 1). The eleven anti-NDUFA11 positive patients showed a trend of lower frequency of wheelchair/walker ever use and higher creatine kinase levels at time of IBM diagnosis compared to the anti-NDUFA11 negative group. Ragged red fibers were significantly more prevalent in anti-NDUFA11 positive than negative patients (p=0.04). Anti-cN1A autoantibodies were detected in 98/287 (34,1%) of IBM, 3/30 (10%) DM and 9/29 (31%) PM patients, p=0.03. Coexistence of anti NDUFA11 and anti-cN1A antibodies was observed in 3 IBM patients.
Conclusion: Our results reveal a new autoimmune target in the mitochondrial respiratory chain complex I that might be specifically associated with IBM. This is of particular interest as mitochondrial abnormalities are known histological findings in muscle biopsies of IBM patients.

REFERENCES:

[1] Galindo-Feria AS, Wang G, Lundberg IE. Autoantibodies: Pathogenic or epiphenomenon. Best Pract Res Clin Rheumatol. 2022;36(2):101767.
[2] Herbert MK,et al. Disease specificity of autoantibodies to cytosolic 5'-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases. Ann Rheum Dis. 2016;75(4):696-701.

Table 1. NDUFA11 protein fragments (PrESTs)

NDUFA11	Amino acid sequence (excluding His6ABP)	PrEST molecular weight (Da) (including His6ABP)
PrEST 1	ASLVKMGRLEGWEVFAKPKV	19833,4
PrEST 2	MAPKVFRQYWDIPDGTDCHRKAYST	20574,06
PrEST 3	TLNPPGTFLEGVAKVGQYTFT	19828,23

Legend: Amino acid sequence and molecular weight of the protein fragments loaded on the western blot gel. NDUFA11, NADH dehydrogenase 1 α subcomplex 11; His6ABP, six histidine and albumin binding protein.

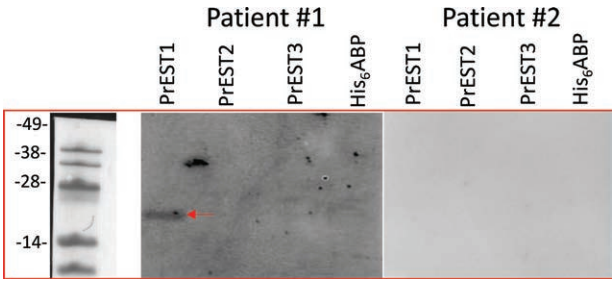

Figure 1. Validation of bead array assay results with western blot

Legend: Western blot showing the reactivity of two IBM patients against the NDUFA11 protein fragments (PrEST1,2,3) expressed with a His6ABP tag. Patient#1 was reactive to PrEST1 and not to PrEST2 and 3 in the bead array assay while patient#2 did not display any reactivity. NDUFA11, NADH dehydrogenase 1 α subcomplex 11; His6ABP, six histidine and albumin binding protein.
Disclosure of Interests: Antonella Notarnicola: None declared, Cecilia Hellstrom: None declared, Begum Horuluoglu: None declared, Charlotta Preger: None declared, Francesco Bonomi: None declared, Boel De Paepe: None declared, Jan De Bleecker: None declared, Anneke J. van der Kooi: None declared, Marianne de Visser: None declared, Sabrina Sacconi: None declared, Pedro Machado: None declared, Umesh A. Badrising: None declared, Anke Rietveld: None declared, Ger Pruijn: None declared, Simon Rothwell: None declared, James B. Lilleker: None declared, Hector Chinoy: None declared, Olivier Benveniste: None declared, Elisabet Svenungsson: None declared, Helena Idborg: None declared, Per-Johan Jakobsson: None declared, Peter Nilsson: None declared, Ingrid E. Lundberg Shareholder of: stock shares in Roche and Novartis, Consultant of: Consulting fees from Corbus Pharmaceuticals, Inc and research grants from Astra Zeneca and has been serving on the advisory board for Astra Zeneca, Bristol Myers Squibb, EMD Serono Research & Development Institute, Argenx, Octapharma, Kezaar, Orphazyme, Pfizer and Janssen.
DOI: 10.1136/annrheumdis-2023-eular.5738

POS0604

ACTIVATION OF TYPE I INTERFERON PATHWAY IN SERA OF PATIENTS WITH ANTI-MELANOMA DIFFERENTIATION-ASSOCIATED GENE 5 ANTIBODY-POSITIVE DERMATOMYOSITIS

Keywords: Myositis, Cytokines and chemokines

S. Nakamura[1], Y. Katsumata[1], Y. Okamoto[1], M. Harigai[1]. [1]*Tokyo Women's Medical University School of Medicine, Division of Rheumatology, Department of Internal Medicine, Tokyo, Japan*

Background: We have previously reported that anti-melanoma differentiation-associated gene 5 (MDA5) antibodies are more frequently associated with rapidly progressive ILD (RP-ILD) and amyopathic dermatomyositis (DM) than anti-aminoacyl-tRNA synthetase (ARS) antibodies and that serum ferritin levels are higher in anti-MDA5-positive patients and serve as a relevant biomarker for RP-ILD [1]. Thus, it is speculated that anti-MDA5 DM and anti-ARS idiopathic inflammatory myopathies (IIMs) have distinct pathomechanisms. It was reported that type I interferon (IFN) gene signature was upregulated in the peripheral blood mononuclear cells and the skin tissues from the anti-MDA5 DM patients [2]. However, the role of type I IFN in anti-MDA5 DM has yet to be fully elucidated.
Objectives: We aimed to determine the activity of IFN-α/β and IFN regulatory factor (IRF) in sera of patients with anti-MDA5 antibody-positive DM with ILD,