**THE ROLE OF D-DIMER TEST AS A SCREENING TOOL FOR VENOUS THROMBOEMBOLISM IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AS COMPARED TO MATCHED CONTROL SUBJECTS**

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**Background:** d-dimer test is widely used as a screening tool for venous thromboembolism (VTE). Meanwhile, d-dimer can increase in various conditions including severe infection, and inflammation. However, it has been rarely reported whether d-dimer test is useful for screening of VTE in systemic lupus erythematosus (SLE) patients.

**Objectives:** We evaluated the role of d-dimer test as a screening tool for VTE in patients with SLE, compared to age- and sex-matched non-autoimmune disease subjects.

**Methods:** In this retrospective cohort study, a total of 283 SLE patients and 1132 age- and sex-matched control subjects (those who had no rheumatic diseases) who underwent d-dimer test as a screening test for VTE were enrolled at Seoul National University Hospital between January 2000 and July 2017. VTE was defined to be present when a thromboembolism was proven in imaging studies which included computed tomography, lung perfusion scan or duplex ultrasonography. Predictive value of d-dimer test for VTE was compared between SLE patients and control subjects by calculating area under the curves (AUC) in receiver operating characteristics (ROC) curves of d-dimer test. Finally, the usefulness of d-dimer test was evaluated in different subsets of SLE patients by analyzing ROC curves.

**Results:** The mean (SD) age of the 283 SLE patients was 36.8 (13.5) years and that of 1132 control subjects was 38.2 (12.8) years. The mean (SD) plasma level of d-dimer was 2262.1 (3794.5) ng/ml in SLE patients, while it was 1087.5 (5063.1) ng/ml in the control group (p < 0.001). The incidence of VTE was significantly higher in SLE patients than the controls (12.7% vs. 5.8%, p < 0.001). When the cut-off value of d-dimer test was set to 500 ng/ml, the AUC for VTE was only 0.614 in SLE patients, while it was 0.891 in the control group, suggesting that d-dimer test may not be useful as a screening tool for VTE in SLE patients. When the SLE patients were divided according to the presence of antiphospholipid antibodies (APS Abs), the AUC for VTE was 0.788 in patients who didn’t have APS Abs but it was only 0.556 in patients who had APS Abs.

**Conclusions:** d-dimer test cannot predict VTE in SLE patients as accurately as in general population. In SLE patients, d-dimer’s diagnostic capability for VTE is even lower in the presence of APS Abs.

**REFERENCES:**


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Systemic sclerosis, myositis and related syndromes – etiology, pathogenesis and animal models.

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THE ATM KINASE AND PTEN, DRIVE MYOFIBROBLASTS DIFFERENTIATION BY ACTIVATING THE TGFβ AUTOCRINE LOOP

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Background: Pulmonary fibrosis is a major cause of mortality in scleroderma (SSc) and Idiopathic Pulmonary Fibrosis (IPF). Fibrosis is driven by Inappropriate myofibroblast differentiation and persistence. Understanding this process, is vital for developing an effective treatment. Angiotensin II is implicated in fibroblast activation in the heart and kidney, through interactions with growth factors (e.g. EGF and TGFβ).

Objectives: We examined the role of Angiotensin II in myofibroblast activation in the lung.

Methods: Lung fibroblasts were isolated from SSc, IPF, or control patient lungs (6 each). Fibroblasts were also cultured from PTEN null and wild-type mice. Protein expression after angiotensin II treatment (AngII) was investigated by western blotting. Myofibroblast differentiation function was assessed through the contraction of 3D collagen gels and scratch migration assays. The signalling pathways involved were dissected using specific inhibitors: PI3 kinase-AKT (wortmannin, LY294002), TGFβ (1d11 neutralising antibody, SB431542 ALK5 inhibitor) Ataxia-Telangiectasia Mutated (ATM – Kufs5933), AngII (Losartan).

Results: SSc and IPF lung fibroblasts showed increased AKT phosphorylation and suppressed PTEN expression (p<0.05). The phenotype was more myofibroblast-like, with higher αSMA expression (p<0.05), increased collagen gel contraction (control; 207±14 vs SSC; 92±15 vs IPF. 91±21, p<0.05), and enhanced migratory capacity (p<0.05). PTEN-null fibroblasts showed a similar phenotype. AngII treatment activated AKT, suppressed PTEN and induced myofibroblast differentiation in normal lung fibroblasts. In both AngII-treated and PTEN lung fibroblasts AKT activation required the ATM kinase. Inhibition of AKT either with PI3K or ATM inhibitor abrogated these effects. The increased expression of Myofibroblast-related genes after AngII treatment, was also blocked by inhibition of TGFβ1 with a neutralising antibody or an ALK5 inhibitor. AKT phosphorylation on the other hand was only partially blocked was partially blocked by TGFβ1 inhibition.

Conclusions: Our data demonstrate for the first time that AngII signals via the ATM kinase, which together with PTEN suppression are essential for the activation of AKT by AngII. AngII promotes myofibroblast differentiation, by stimulating the fibroblast TGFβ1 autocrine loop through AKT. Our data shows that activation of AKT through ATM and PTEN, may serve as the molecular link between pulmonary hypertension and lung fibrosis in fibrotic diseases.

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PECCULAR EXPRESSION OF AUTOAPHTHAGY BIOMARKERS IN NECROTIZING AUTOIMMUNE MYOPATHY MUSCLE

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Background: Immune mediated necrotizing myopathy (IMNM) is a recently recognised pathology within the spectrum of idiopathic inflammatory myopathies (IMMs). Specific autoantibodies and the response to immunosuppressants aid to make the diagnosis and suggest immune-mediated pathogenesis, although histopathological features are not specific for IMNM. Autoapthy and ubiquitin-proteasome system are two interacting systems by which dysfunctional cellular components are degraded in the cell. Their dysregulation, in sporadic inclusion

Body Myositis (sIBM), seems to be responsible for the protein aggregates. The autoapthy dysfunction in IMNM was not widely investigated.

Objectives: To investigate autoapthy marker expression, macrophages localization and accumulation of misfolded proteins in non-necrotic fibres of IMNM muscle in comparison with Dermatomyositis (DM), Polymyositis (PM) and sIBM.

Methods: Among 52 IIMs diagnosed from January 2015 to June 2017, we reviewed muscle biopsies and stored sera. Six subjects were included in the IMNM group, characterised by many necrotic muscle fibres, regenerating muscle fibres and no significant inflammation despite of numerous but scattered macrophages removing necrotic muscle fibres. Two patients had anti-signal recognition particle (SRP) autoantibodies, two patients anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the others tested negative for specific autoantibodies. All IMNM patients had a positive response to immunosuppressants. Muscle sections were immunolabelled with the following antigens: ubiquitin, autoapthy markers LC3b, p62 (a receptor of autophagy), LC3b -puncta (Phosphorylated Neurofilaments), CD31 (endothelial cell marker), C5b-9 (membrane attack complex), CD4 (T-helper lymphocytes), CD8 (T-suppressor lymphocytes), CD68 (macrophages), CD20 (B-lymphocytes), CD56 (NK lymphocytes and regenerating muscle fibres), MHC I, MHC II. Quantitative results were compared among IMNM (n=6), DM (n=4), sIBM (n=4), PM (n=5) and healthy controls (n=4).

Results: In IMNM, inflammation was mild compared with DM, PM, sIBM, and consisted in sporadic endomysial and/or perivascular cells CD68+. Skeletal muscle fibres (SMFs) containing LC3b+puncta were significantly higher in IMNM and IMMs than in DM or PM. In all IMNM, the greater proportion of LC3b+puncta was localised in CD68+ fibres (figure 1), instead, sIBM showed a high number of LC3b+puncta in vacuolated SMFs with low expression of CD65 +SMFs. As expected, p62 and SM31 aggregates were significantly higher in sIBM than in the other IIMs, even if, also in IMNM, there were moderate p62 accumulations and a little proportion of SMFs stained by SM31. Finally, in IMNM there was the highest number of ubiquitin +SMFs.

Conclusions: These findings suggest an involvement of cellular clearance systems in the pathophysiology of IMNM similar to sIBM. Nevertheless, LC3b+puncta in regenerating fibres can be considered a peculiar biomarker in IMNM. Further studies of larger cohort of patients are needed to better define IMNM.

Disclosure of Interest: None declared


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SL-401, A NOVEL TARGETED THERAPY DIRECTED TO THE INTERLEUKIN-3 RECEPTOR (CD123), KILLS PLASMACYTOID DENDRITIC CELLS FROM SYSTEMIC SCLEROSIS PATIENTS

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Background: SL-401 is a novel biologic targeted therapy directed to the interleukin-3 receptor (CD123), kills plasmacytoid dendritic cells from systemic scleroderma patients.

Further studies of larger cohort of patients are needed to better define IMNM.

Disclosure of Interest: None declared
