AB0907 HIGH EXPRESSION LEVELS OF TYPE I INTERFERON AND IP-10 IN ANTI-MDA5 ANTIBODY-POSITIVE DERMATOMYOSITIS AND ITS IMPLICATION IN THE PATHOGENESIS

Keywords: Myositis, Cytokines and chemokines, Biomarkers

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Background: Dermatomyositis (DM) patients with anti-melanoma differentiation-associated protein 5 (MDA5) antibodies (Ab) are likely to have rapidly progressing interstitial lung disease and a poor prognosis. Thus, it is important to understand the pathogenesis of the disease.

Objectives: The aim of this study was to identify humoral factor(s) that characterize anti-MDA5 Ab+ DM and to analyze the cells that produce these factors.

Methods: Twenty-eight cytokines in the serum of patients with anti-MDA5 Ab+ DM patients were screened and compared with the results of patients with other collagen vascular diseases. We also performed an immunohistochemical analysis of skin rashes (Gottron’s signs) from two patients.

Results: Serum levels of interferon-gamma-induced protein 10 (IP-10, CXCL10), one of CXCR3 chemokines, were significantly higher in anti-MDA5+ DM patients than in SLE and anti-MDA5 Ab- DM patients. Moreover, serum interferon (IFN) α2 levels were also higher in anti-MDA5+ DM patients. After initiation of immunosuppressive therapy, IP-10 and IFN-α2 levels decreased rapidly, whereas those of IFN-γ and CXCL9, another CXCR3 chemokine, did not substantially decrease. Skin samples revealed that the IP-10 positive cells in the dermis were positive for CD68 antigen, a monocyte/macrophage marker. In contrast, they contained a few CD8+ cells and almost no CD4+ cells. We also stimulated monocytes from healthy controls with type I and II IFNs in vitro and demonstrated that IP-10 was produced in the culture supernatant in a dose-dependent manner.

Conclusion: Our results indicate that IP-10 is highly produced in DM patients with anti-MDA5 Abs. The levels of type I IFN were also high and even exceeded those of SLE. Several reports have shown that not only type II IFN but also type I IFN induces IP-10. Thus, type I IFN/IP-10 axis may play an important role in the pathogenesis of anti-MDA5 Ab+ DM. Our immunohistochemical analysis of the skin also revealed that IP-10 released from macrophages may prompt infiltration of macrophages themselves, constituting a positive feedback loop in the skin inflammation. Further analyses are required to prove the usefulness of IP-10 as a disease activity and/or prognostic marker of DM with anti-MDA5 Abs.


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AB0908 SCREENING AND ANALYSIS OF POSSIBLE DRUGS BINDING TO PDGFRα: A MOLECULAR MODELING STUDY

Keywords: Targeted synthetic drugs, Systemic sclerosis, Disease-modifying Drugs (DMARDs)

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Background: The platelet-derived growth factor receptor (PDGFR) is a membrane tyrosine kinase receptor involved in several metabolic pathways, mainly in tumor progression [1, 2], immune-mediated diseases [3-4], and viral diseases [5].

Objectives: Considering this macromolecule as a druggable target for modulation/inhibition of these conditions, the aim of this work was to find new ligands or new information to design novel effective drugs.

Methods: We performed an initial interaction screening with the human intra-cellular PDGFRα of about 7200 drugs and natural compounds contained in five independent databases, implemented in the MTI/OpenScreen web server. After selection of 27 compounds, a structural analysis (in particular, molecular docking and molecular dynamics analysis, using SwissDock based on EADock DSS algorithm [6, 7] and GROMACS [8], respectively) of the complexes obtained was performed. Three-dimensional quantitative structure–activity relationship and ADMET analyses were also performed to understand physicochemical properties of that compound to increase affinity and selectivity.

Results: Among these 27 compounds, the drugs Bafetinib, Radotinib, Flumatinib and Imatinib showed the higher affinity for this tyrosine kinase receptor, lying in the nanomolar order, while the natural products, such as curcumin, luteolin and EGCG, included in this group showed submicromolar affinities. All these compounds, through the QSAR and ADMET analysis, provided physicochemical information about an ideal best ligand for PDGFRα.

Conclusion: Although experimental studies are recommended, the structural information obtained could provide useful insight into the future development of PDGFRα inhibitors.

REFERENCES:

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AB0909 IMMUNOEXPRESSION OF TGFß1 IN SKIN IN SYSTEMIC SCLEROSIS

Keywords: Prognostic factors, Systemic sclerosis, Diagnostic Tests

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Background: TGF-ß1 pleiotropic functions in inflammation, fibrosis, and vascular remodeling suggest that TGF-ß1 signaling could play a central role as a link between fibrosis and vasculopathy characteristic of SSc. Moreover high mRNA level of TGF-ß1 in whole blood and high immunoreexpression in tissues in SSc patients confirms its role in the SSc pathogenesis.

Objectives: The aim of this study was to determine TGFß1 immunoeexpression in the skin of patients with systemic sclerosis.

Methods: Skin biopsies from 14 patients with SSc (7 female and 7 male) at median age 60 years (19-69) were analyzed by immunohistochemistry method using anti-TGFß1 primary mouse monochlonal antibody IgG (Abcam, Cambridge, UK, ab195005). Morphological analysis has been conducted by Hematoxylin and eosin (H&E) staining and Masson trichrome staining. The sections were examined using a light microscope Olympus BX 41 (Olympus, Hamburg, Germany).

Patients. Women and men in the study group did...