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HSP90 IN AXIAL SPONDYLOARTHRITIS, PSORIATIC ARTHRITIS AND RHEUMATOID ARTHRITIS

^{1,2}H Storkanova*, ^{1,2}K Bubova, ^{1,2}S Oreska, ³M Spiritovic, ³B Hermankova, ^{1,2}M Gregorova, ^{1,2}K Mintalova, ¹J Horinkova, ^{1,2}K Pavelka, ^{1,2}J Vencovsky, ^{1,2}J Stofa, ^{1,2}M Husakova, ^{1,2}S Forejtova, ^{1,2}L Senolt, ^{1,2}M Tomcik. ¹Institute of Rheumatology, Prague, Czech Republic; ²Department of Rheumatology, 1st Faculty of Medicine, Institute of Rheumatology; ³Faculty of Physical Education and Sport, Department of Physiotherapy, Charles University, Prague, Czech Republic

10.1136/annrheumdis-2018-EWRR2019.153

Career situation of first and presenting author Student for a master or a PhD.

Introduction Hsp90 is a highly conserved molecular chaperone that regulates activation of innate immunity, antigen presentation, and the induction of proinflammatory cytokines and chemokines. These properties predispose Hsp90 to its potential role in the pathogenesis of autoimmune inflammatory rheumatic diseases.

Objectives The aim of this study was to assess plasma Hsp90 in patients with axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), rheumatoid arthritis (RA) and healthy controls (HC) and to determine its potential association with disease activity and clinical features.

Methods A total of 136 patients, that were divided into groups according to the type of a rheumatic disease (SpA, RA, PsA), and age-/sex- matched healthy individuals were included. Plasma Hsp90 levels were measured by ELISA (eBioscience, Vienna, Austria). Data are presented as median (IQR).

Results Plasma Hsp90 levels were significantly increased in axSpA and in RA patients compared to HC. The increased plasma levels of Hsp90 in PsA compared to HC did not reach statistical significance. Hsp90 concentrations were higher in RA patients with an altered serum lipid profile: low-density lipoprotein (LDL: $r=0.352$, $p=0.048$), high-density lipoprotein (HDL: $r=-0.349$, $p=0.046$) and atherogenic index (calculated as $\log(\text{triglycerides}/\text{HDL})$) (AI: $r=0.454$, $p=0.009$). Furthermore, Hsp90 levels in r-axSpA patients positively correlated with the MRI presence of active inflammatory lesions in sacroiliac joints (SPARCC MRI score for SI joints: $r=0.594$, $p=0.020$). Increased Hsp90 levels in PsA patients were associated with the count of joint deformities ($r=0.526$, $p=0.025$). No further statistically significant associations were found between Hsp90 plasma levels and RA-, axSpA- or PsA-specific clinical features.

Conclusions We demonstrated elevated plasma concentrations of Hsp90 in RA and in axSpA patients compared to healthy controls. Hsp90 could be associated with early alterations of serum lipids and development of atherosclerosis in RA. Furthermore, in r-axSpA, Hsp90 may represent an independent marker of SI joint inflammation, whereas in PsA, plasma Hsp90 correlates with joint deformities. These data suggest that Hsp90 could become a potential biomarker of structural changes in SpA.

REFERENCE

None.

Acknowledgements Supported by AZV-16-33542A and MHCR 023728.

Disclosure of Interest None declared.

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NLRP3 INFLAMMASOME-MEDIATED PYROPTOSIS AGGRAVATES THE AIRWAY INFLAMMATION IN TOLUENE DIISOCYANATE-INDUCED ASTHMATIC MICE

¹J Zhuang, ¹Y He, ²H Cui, ¹E Sun*, on behalf of Guihu Luo, Fangyuan Yang, Juan He, Zeqing Zhai, Haijin Zhao, Wenqu Zhao. ¹Department of Rheumatology and Immunology; ²Department of Respiratory and Critical Care Medicine, The Third Affiliated Hospital of Southern Medical University, Guangzhou, China

10.1136/annrheumdis-2018-EWRR2019.154

Career situation of first and presenting author Young investigator.

Introduction NLRP3 inflammasome-mediated pyroptosis is a highly inflammatory event. This cell death process is characterized by cell explosion and IL-1 β release.¹ Our previous data have revealed that NLRP3 inflammasome-mediated pyroptosis plays an essential role in the pathogenesis of collagen-induced arthritis mice and lupus-like mice. While blockade of NLRP3 inflammasome-mediated pyroptosis alleviates the inflammation and organ damage in these autoimmune mice models.

Objectives Interesting, Toluene diisocyanate(TDI), the most common organic compound causing occupational asthma, has been proven to drive bronchial epithelium damage and IL-1 β production in patients with TDI-induced asthma. Therefore, in this study, we investigated whether NLRP3 inflammasome-mediated pyroptosis was involved in bronchial epithelial injury and airway inflammation in TDI-induced asthma.

Methods *In vitro*, 16HBEs (a human bronchial epithelial cell line) were stimulated with TDI. Then the cell death form was identified. *In vivo*, TDI-induced asthmatic mice were established after sensitization and challenge with TDI. After treatment with the NLRP3 inflammasome specific inhibitor, the airway hyperresponsiveness (AHR) and airway inflammation in asthmatic mice were assessed.

Results Here we found that TDI induced 16HBEs pyroptosis in a time and dose-dependent manner, as evidenced by the increased ratio of caspase-1⁺PI⁺ cells and the enhanced levels of LDH and IL-1 β . Importantly, the NLRP3 inflammasome specific inhibitor significantly blocked TDI-induced pyroptosis. In TDI-induced asthmatic mice, NLRP3 inflammasome inhibitor attenuated AHR and airway inflammatory infiltration by inhibiting the activation of caspase-1 and the cleavage of pyroptotic executioner GSDMD in the lungs. Moreover, NLRP3 inflammasome inhibitor decreased the levels of IL-1 β in the plasma and bronchoalveolar lavage fluid (BALF), accompanied by lower level of IgE in the plasma and Th2-related cytokines in the BALF.

Conclusions Our data demonstrated for the first time that bronchial epithelial pyroptosis was critical for TDI-induced asthma pathogenesis via the activation of NLRP3 inflammasome and the cleavage of GSDMD. Inhibition of NLRP3 inflammasome-mediated pyroptosis may be a valuable therapeutic strategy for TDI-induced asthma.

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Acknowledgements This work was supported by National Natural Science Foundation of China (81501417, 81671623, 81873880), Medical Scientific Research Foundation of Guangdong Province, China (A2016492) and Science and Technology Planning Project of Tianhe District, Guangzhou City (201504KW037).

Jian Zhuang and Yi He contributed equally as co-first authors.

Haiyan Cui and Erwei Sun are corresponding authors.

Disclosure of Interest None declared.

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COMPLEX ASSESSMENT OF BONE MINERAL DENSITY, FRACTURE RISK, VITAMIN D STATUS AND BONE METABOLISM IN HUNGARIAN SYSTEMIC SCLEROSIS PATIENTS

¹Z Szekancz*, ¹Á Horváth, ¹E Végh, ¹A Pusztai, ¹Z Pethő, ¹A Hamar, ²HP Bhattoa, ²G Nagy, ³B Juhász, ¹K Hodosi, ¹A Domján, ¹G Szűcs, ¹S Szamosi. ¹Department of Internal Medicine, Division of Rheumatology; ²Department of Laboratory Medicine; ³Department of Oncology, University of Debrecen, Faculty of Medicine, Debrecen, Hungary

10.1136/annrheumdis-2018-EWRR2019.155

Career situation of first and presenting author Instructor.

Introduction Osteoporosis has been associated with systemic sclerosis (SSc).

Objectives We wished to determine bone alterations in SSc patients by conventional densitometry (DXA), peripheral quantitative computed tomography (pQCT) and bone biomarkers.

Methods We included 44 SSc patients and 33 age-matched healthy controls. Lumbar spine and femoral neck bone mineral density (BMD) was assessed by DXA. Volumetric BMD was measured by pQCT at the radius. FRAX, 25-hydroxyvitamin-D₃ (25-OH-D₃), parathyroid hormone, osteocalcin, C-terminal collagen telopeptide and procollagen type I amino-terminal propeptide were also assessed.

Results SSc patients had lower L2–4 BMD (0.880 ± 0.108 vs. 0.996 ± 0.181 g/cm²; $p=0.019$) and femoral neck (FN) BMD (0.786 ± 0.134 vs. 0.910 ± 0.090 g/cm²; $p=0.007$) by DXA. In SSc vs controls, pQCT indicated lower mean cortical (328.03 ± 103.32 vs 487.06 ± 42.45 mg/cm³; $p<0.001$) and trabecular density (150.93 ± 61.91 vs 184.76 ± 33.03 mg/cm³; $p=0.037$). Vitamin D₃ deficiency was more common in SSc vs controls (60.0% vs 39.3%; $p=0.003$). L2–4 ($p=0.002$) and FN BMD ($p=0.015$) positively correlated with BMI. pQCT assessments confirmed an inverse correlation between pulmonary manifestation and total ($p=0.024$), trabecular ($p=0.035$) and cortical density ($p=0.015$). Anti-Scl70 positivity inversely correlated with pQCT total density ($p=0.015$) and the presence of digital ulcers with cortical density ($p=0.001$). We also found that vertebral and FN BMD as determined by DXA significantly correlated with pQCT total, trabecular and cortical density ($p<0.05$).

Conclusions The results of our study suggest that bone loss in SSc patients may be associated with lower BMI, anti Scl70 positivity, and the presence of pulmonary manifestations and digital ulcers. Both DXA and pQCT are appropriate tools to evaluate the bone alterations in SSc patients.

Acknowledgements This research was supported by Hungarian National Scientific Research Fund (OTKA) grant No. K 105073 (H.P.B. and Z.S.); by the European Union and the State of Hungary and co-financed by the European Social Fund in the framework of TAMOP-4.2.4.A/2-11/1-2012-0001 'National Excellence Program' (Z.S.); by the European Union grants GINOP-2.3.2-15-2016-00015 and GINOP-2.3.2-15-2016-00050 (Z.S.).

Disclosure of Interest None declared.

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TRANSMEMBRANE TNF TRANSGENIC MICE EXHIBIT ENLARGED LYMPH NODES AND ELEVATED NUMBERS OF HIGH ENDOTHELIAL CELLS ASSOCIATED WITH INCREASED LYMPHOCYTE RECRUITMENT

KC Jeucken, JP van Hamburg, MH Kaaij, LM van Duivenvoorde, DL Baeten, SW Tas*. *Experimental Immunology/Clinical Immunology and Rheumatology, Amsterdam UMC, Amsterdam, Netherlands*

10.1136/annrheumdis-2018-EWRR2019.156

Career situation of first and presenting author Post-doctoral fellow.

Introduction NF- κ B signaling plays a crucial role in chronic inflammatory diseases and can be activated via two pathways. Noncanonical NF- κ B signaling can be induced by different signals, including transmembrane (tm)TNF ligation to TNF receptor 2 (TNFR2), which is restricted to specific cell types including endothelial cells (EC). Activation of the noncanonical NF- κ B pathway in EC is involved in differentiation into high endothelial cells (HEC), which make up specialized high endothelial vessels (HEV) that recruit lymphocytes into lymph nodes (LN). tmTNF transgenic (tg) mice overexpressing tmTNF develop chronic inflammatory features, including arthritis and axial inflammation.

Objectives To study LN size and composition, including stromal cell and lymphocyte subsets in tmTNF tg mice. We hypothesized that overexpression of tmTNF results in increased noncanonical NF- κ B signaling in HEC leading enhanced lymphocyte recruitment.

Methods Peripheral (PLN) and mesenteric LN (MLN) of 7 week old tmTNF tg mice and age-matched wild types (WT) were collected, dissected and analyzed using flow cytometry. Cellular markers were used to distinguish between different EC subsets, and B and T lymphocytes.

Results Lymph nodes of tmTNF tg mice had more than two-fold increased total cell numbers compared to WT (PLN: $23,7 \times 10^6 \pm 7,9 \times 10^6$; MLN: $24,9 \times 10^6 \pm 5,3 \times 10^6$. WT PLN: $5,2 \times 10^6 \pm 1,0 \times 10^6$; MLN: $10,4 \times 10^6 \pm 4,6 \times 10^6$). Total numbers of HEC in tmTNF tg mice LN were increased (PLN: $2,3 \times 10^3 \pm 0,50 \times 10^3$; MLN: $1,9 \times 10^3 \pm 0,64 \times 10^2$. WT PLN: 714 ± 393 ; MLN: 1.199 ± 506), as were capillary EC (CEC) numbers (PLN: 2067 ± 42 ; MLN: 2425 ± 71 . WT PLN: 1097 ± 609 ; MLN: 1327 ± 230). Notably, HEC:CEC ratio was increased in tmTNF tg mice (PLN: $1,10 \pm 0,241$. WT PLN: $0,66 \pm 0,006$). In addition, total B and T lymphocytes in tmTNF tg mice LN were strongly increased (B lymphocytes: PLN: $10,2 \times 10^6 \pm 3,5 \times 10^6$; MLN: $10,9 \times 10^6 \pm 1,8 \times 10^6$. WT PLN: $2,8 \times 10^6 \pm 5,8 \times 10^5$; MLN: $5,8 \times 10^6 \pm 2,4 \times 10^6$. T lymphocytes: PLN: $12,8 \times 10^6 \pm 4,5 \times 10^6$; MLN: $14,2 \times 10^6 \pm 2,8 \times 10^6$. WT PLN: $2,5 \times 10^6 \pm 3,8 \times 10^5$; MLN: $4,7 \times 10^6 \pm 2,1 \times 10^6$).

Conclusions Overexpression of tmTNF in mice leads to an increase in total HEC, CEC and lymphocyte numbers and an increased HEC:CEC ratio in PLN and MLN. The increase in HEC may be the result of enhanced noncanonical NF- κ B signaling, enhancing lymphocyte recruitment into the LN. Consequently, interfering with noncanonical NF- κ B signaling in EC may be a promising treatment strategy to dampen inflammation in immune-mediated inflammatory diseases, which is the subject of current studies.

Disclosure of Interest None declared.