Inflammatory monocyte-derived dendritic cells mediate autoimmunity in murine model of systemic lupus erythematosus

T Masuda1, K Iwasaki2, H Enomoto3, M Matsuoka4, M Takahara2,5, A Aihara2, M Takahashi2, T Kubo2, H Kiyono6, Y Yamada1,2,3,4 and S Yokoyama1,2,3,4

1Department of Dermatology, Nara Medical University, Kashihara, Nara, Japan
2Basic Medical Science, University of Tokyo, Tokyo, Japan
3Vaccine Research Center, Tokyo Institute of Technology, Tokyo, Japan
4Laboratory of Infection and Immunity, RIKEN Center for Life Science, SPring-8, Hyogo, Japan
5Department of Dermatology, Shinshu University School of Medicine, Matsumoto, Nagano 390-1192, Japan
6Department of Dermatology, Juntendo University School of Medicine, Tokyo, Japan

Using a mouse model of systemic lupus erythematosus (SLE) induced by 2,6,10,14-tetra-methylpentadecane (TMPD), we recently demonstrated that IRF7-deficient mice developed glomerulonephritis whereas IFN-β−/− mice developed autoantibody production. We suggested that the major manifestations of SLE are mechanistically independent because the type I interferon (IFN) pathway leads to the autoantibody production whereas the NF-κB activation is sufficient for the development of glomerulonephritis. To further advance our understandings on the molecular pathways regulating the development of SLE, we studied the role of IFNβ because it controls both type I IFN and NF-κB pathways and saw that IRF7-deficient mice failed to develop either glomerulonephritis or the autoantibody production. Furthermore, these genetic differences did not appear to result from differences in the monocyte/macrophage populations. In conclusion, we demonstrated that monocyte/macrophage dysfunction is sufficient to drive the development of systemic lupus erythematosus.

025 Extracellular vesicles induce STING-mediated proinflammatory cytokines in Dermatomyositis

Y Li, C Bax, M Bashir, K Desai, M Zeidli and V Werth

University of Pennsylvania, Pennsylvania, United States

Dermatomyositis (DM) is an acquired inflammatory myopathy characterized by chronic skin inflammation. The pathogenesis of DM is still unclear. Extracellular vesicles (EVs) are lipid bilayer membrane vesicles existing in various bodily fluids and implicated in the pathogenesis of autoimmune diseases. As type I interferons, specifically IFNβ, are uniquely elevated in DM, and Stimulator of interferon genes (STING) works as a critical sensor and adaptor in type I IFN signaling, we hypothesized that EVs derived from DM patients’ plasma might trigger STING-mediated proinflammatory effects. DM patients were recruited in the dermatology clinic at U Penn. Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll gradient. EVs derived from plasma were isolated via ultracentrifugation. The supernatant was harvested for ELISA and the lysed cells were used for Western blot and qPCR. PBMCs were stimulated by EVs. We found that DM patients’ plasma-derived EVs triggered cytokines release (IFNβ: 30.24 ± 0.65 vs control: 2.63 ± 0.15; TNFα: 1451 ± 98.0 vs control: 16.75 ± 1.40 pg/ml; n=6) with STING phosphorylation. Inhibition of STING significantly attenuated DM patients’ plasma derived EVs-triggered cytokines production (IFNβ: 21.58±2.22 vs 22.34±1.73; TNFα: 434 ± 9.4 ± 5.50 vs 191.1 ± 1.13 pg/ml; n=6) via suppressing STING and its downstream signal STK1, IRF3, and NIFκB phosphorylation. To further explore whether STING phosphorylation and the proinflammatory effects were not only caused in the pathogenesis of the disease but also in flare-ups of the disease.

026 Increased levels of high mobility group box 1 in the serum and skin in patients with generalized pustular psoriasis

T Watanabe, Y Yamaguchi, Y Watanabe, N Takamura and M AIhara Dermatology, Yokohama City University Medical School, Japan

High mobility group box 1 (HMGB-1) is a highly abundant pro-inflammatory protein which is associated with the pathogenesis of inflammatory and autoimmune diseases, such as drug eruption, sepsis, and rheumatoid arthritis. HMGB-1 has a dual function: inside the cells, it is associated with the transcription regulation. While outside the cells, it plays an alarming or a damage-associated molecular pattern. It has been reported that HMGB-1 expression levels in the serum and skin were increased in patients with psoriasis vulgaris (PV). However, HMGB-1 expression in patients with generalized pustular psoriasis (GPP) was unknown. In this study, we investigated the HMGB-1 levels in the serum and skin in patients with GPP. To analyze the expression levels of HMGB-1, we performed ELISA and immunohistochemistry in the skin biopsies of patients with GPP along with control (HC). Immunohistochemistry analysis revealed that HMGB-1 expression levels in epidermis were significantly increased in patients with GPP compared to that in patients with PV, AD and HC. In addition, patients with GPP had elevated serum HMGB-1 levels compared to AD patients and HC. Furthermore, serum levels of HMGB-1 were significantly decreased after the systemic treatment compared to baseline levels. In the correlation analysis, a high positive correlation was detected between serum HMGB-1 levels and Japanese severity criteria for GPP in patients with GPP. In conclusion, our findings show that HMGB-1 might be used in the pathogenesis of GPP and is a simple and attractive marker for the analysis of disease severity and the effectiveness of treatment in patients with GPP.