007 Essential requirement for IRF7 in autoantibody production but not development of glomerulonephritis in murine lupus

T Mizoguchi and H Asada Department of Dermatology, Nara Medical University, Kashihara, Japan

Using a murine model of systemic lupus erythematosus (SLE) induced by 2,6,10,14-tetramethyl-2,6,10,14-pentaoxacyclooctadecane (TMC) or TMC-P, we previously reported that interferon regulatory factor 7 (IRF7) deficient mice failed to produce autoantibodies such as anti-dsDNA, sDNa, rNPl and Sm autoantibodies. TMC-P induced apoptosis similarly in wild-type (WT) and IRF7 deficient mice, suggesting that the dysregulation of apoptosis was not involved in the pathogenesis of SLE-like symptoms in these mice. Total IgG and IgM levels did not differ significantly between WT and IRF7 deficient mice after TMC-P injection suggesting a specific requirement for IRF7 in autoantibody production. However, the lack of these autoantibodies did not affect the development of glomerulonephritis confirming the importance of IRF7-deficient mice. These results suggest that type I IFN pathway was critical in autoantibody production but IFN-deficient activation was sufficient for development of glomerulonephritis. Therefore, these data demonstrate that autoantibody production and tissue pathology involve overlapping but not identical transcription pathways and that these two events can at times take place independent of each other. We propose that a concurrent inhibition of these multiple pathways might be an excellent strategy to prevent and treat human SLE.

008 VGLL1 is a key regulator of transcriptome changes in gender biased autoimmune conditions

Y Horisaka1, Y Kase1, Y Yamagami1, W Yoda1, S Konya1, H Takahashi1 and M Amagai2 1 Dept. Dermatol., Keio Univ, Tokyo, Japan, 2 Japan Blood Products Organization, Tokyo, Japan

Emerging evidence has demonstrated that Toll-like receptors (TLRs) are associated with autoimmune diseases. Men and women differ in their regulation of immune responses. Many autoimmune diseases, ranging from systemic disorders, such as systemic lupus erythematosus (SLE), to organ-specific diseases, such as Grave’s disease, feature a greater prevalence in females than in males (female: male, SLE: 9:1 and Grave’s disease: 7:1). Understanding the cause of female-biased susceptibility to autoimmune conditions is critical to developing preventative measures in high-risk populations. Through the use of high-resolution global transcriptome analyses, we demonstrated a female-biased molecular signature in skin that is associated with susceptibility to autoimmune diseases (Spearman coefficient p = 0.81, P < 1.5E-2). Sex differences in human skin further extended beyond the differentially expressed genes to their associated, co-expression networks (124,521 gene pairs showed significance in females only and 158,101 gene pairs in males only, FDR < 0.05). This female-biased, autoimmune gene signature was independent of biological age and sex-hormone regulation and was transfected using VGLL1 (0.95) which also displayed a female-biased expression (P < 0.05). On a genome-wide level, VGLL1-regulated genes had a strong association with multiple autoimmune diseases, including lupus, scleroderma and Sjögren’s syndrome (P < 0.05). VGLL1 was also required for the optimal response to interferons in monocytes and salivary gland cells (P < 0.05). Our results uncovered a sex-hormone-independent mechanism that predisposes females to autoimmune diseases, and they provided a foundation for the development of novel, targeted treatment measures.

009 B10 cells suppress contact dermatitis in an antigen specific manner

M Kamata1, KM Candando2, E Kountikov2, A Yoshizaki3, T Miyagaki4, JM Lykken2, F Miyagawa and H Asada

1 Department of Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan, 2 Department of Dermatology, University of Tokyo, Tokyo, Japan, 3 RIKEN Center for Integrative Medical Sciences, Tokyo, Japan, 4 Keio Univ, Tokyo, Japan, and 5 Dept. Dermatol., Keio Univ / RIKEN-IMS, Tokyo, Japan

Contact dermatitis has not been reported. Furthermore, several signaling pathways are involved in inflammation through downregulation of regulatory T cells and impaired IL-10 production by regulatory T cells and dendritic cells. Despite this well-characterized pro-inflammatory B cell function, a rare target for gene therapy, one might be that dendritic cells negatively regulate inflammation and autoimmunity by producing anti-inflammatory cytokines (IL-10) and regulatory T cells. However, TLR 2 signaling directly upregulates the prolif-

010 FcgRIIb is important for clonal ignorance and prevents pemphigus phenotype in pathogenic anti-desmoglein 3 antibody knock-in mice

H Nomura1, Y Kase1, J Yamagami1, N Wada1, S Konya1, H Takahashi1 and M Amagai2 1 Dept. Dermatol., Keio Univ, Tokyo, Japan, 2 Japan Blood Products Organization, Tokyo, Japan

FcgRIIb is important for clonal ignorance and prevents pemphigus phenotype in pathogenic anti-desmoglein 3 antibody knock-in mice. We previously generated pathogenic anti-Dsg3 IgG, AK2, knock-in mice which can potentially undergo class switch recombination of IgM immunoglobulin. However, AK2 mice did not develop PV phenotype in steady state, suggesting tolerance mechanisms in the mice. We here investigated the role of FcgRIIb in regulating tolerance mechanisms, including deletion, anergy, receptor editing, and clonal ignorance. The purpose of this study is to clarify which mechanism is important in AK2 mice. Bone marrow (BM) cells from AK2 mice were transferred into recipient mice which resulted in analysis of the clonal ignorance state of AK2 mice. To clarify clonal ignorance state of AK2 mice in the presence or absence of FcgRIIb. AK2 mice were used to develop BM and spleen similarly between both recipients. AK2 mice from both recipients similarly responded upon anti-Dsg3 antibody stimulation. These results suggested that AK2 mice were not deleted or anergic, instead stayed in “clonal ignorance”. To further understand whether FcgRIIb contributes to this state, AK2 mice were used with FcgRIIb-deficient allele. AK2-1K11 mice were introduced with FcgRIIb-deficient allele. AK2-1K11-FcgRIIb mice spontaneously developed PV phenotype, such as skin erosions, acantholysis, and IgG deposition on keratinocyte surfaces with higher levels of anti-Dsg3 IgG compared to AK2 mice. Their survival rate at age of 12 weeks was also significantly lower than that of AK2 mice (39% vs 81%, p = 0.005), further indicating break-down of clonal ignorance in FcgRIIb deficient mice. FcgRIIb plays an important role in maintaining clonal ignorance and preventing the development of PV phenotype in AK2 mice.