THE PATHOGENIC RELEVANCE OF T FOLLICULAR REPOSITORY CORTICOTROPIN INJECTION EXERTS DIRECT ACUTE EFFECTS ON HUMAN B CELL GENE EXPRESSION DISTINCT FROM THE ACTIONS OF GLUCOCORTICOIDS

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Background and aims Repository corticotropin injection (RCI; H.P. Acthar Gel) is a porcine pituitary-derived ACTH preparation approved by the FDA for therapy in selected cases of SLE. Previous studies have shown that RCI directly inhibits human B cell function in vitro.

Methods We used RNA-Seq to identify elements of the transcriptome that are acutely modulated by RCI in human B cells activated in vitro by IL4 and CD40 ligand. We compared RCI effects to those of a synthetic glucocorticoid (dexamethasone; Dex) under the same conditions.

Results 115 unique gene transcripts were significantly and reproducibly upregulated by RCI after 24 hours in culture. Pathways analysis revealed that upregulated genes were over-represented in “immune system response” (2.8-fold; p=0.026) and “response to stress” (4.16-fold; p=0.0069). 74 gene transcripts were down-regulated by RCI, and these were over-represented in two pathways: “immune system response” (2.91-fold; p=0.035) and “cellular process” (1.73-fold; p=0.0036). In Dex-treated cells, 65 gene transcripts were upregulated and 23 gene transcripts were down-regulated. There was no overlap between the sets of genes upregulated by RCI and Dex. Two genes (PARM1 and RANKL) were downregulated by both RCI and Dex. Pathways analysis of Dex- treated samples did not reveal significant overrepresentation of regulated genes in any specific ontologic pathway.

Conclusions These data suggest that RCI exerts direct effects on human B cells to acutely modulate gene expression. These effects are distinct from those of glucocorticoids, supporting potential differences in mechanism of action of these two agents for treatment of autoimmune diseases.

Background and aims Autoantibodies targeting Ro52 occur in systemic lupus erythematosus, Sjogren’s syndrome and idiopathic inflammatory myopathies. Yet the most compelling evidence for their pathogenesis is the development of cardiac conduction abnormalities, a manifestation of neonatal lupus, in

Determining the pathogenic relevance of Ro52 autoimmune antibodies in patients with systemic lupus erythematosus

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Background and aims The increased Tregs apoptosis was negatively correlated with the total number of Tregs and positively correlated with disease activities. Microarray profiles of Tregs from SLE subjects reveal a cellular response that could make the cells sensitive to apoptosis, partially due to the stress responses, DNA-damaging and cytokine stimulation.

Conclusions This global picture of pathway-specific expression signatures is a step further dissecting Treg cell defects in the pathogenesis of SLE, and may shed light on the newly therapeutic strategies towards the aberrant Treg apoptosis and reconstruction of SLE immune homeostasis.

Background and aims The aim of this study was to assess the peripheral immune cell phenotypes in a correlation with clinical findings in patients with systemic lupus erythematosus (SLE).

Methods Peripheral blood mononuclear cells were obtained from 143 SLE patients and 26 healthy donors (HD). Circulating B, T and dendritic cells were defined based on flow cytometric analysis for human immune system termed “the Human Immunology Project” proposed by the National Institutes of Health (NIH) and the Federation of Clinical Immunology Societies (FOCIS).

Results The proportions of CD3+CD4+CXCR5+ICOS+ T follicular helper (Tfh) cells, but not CD3+CD4+CXCR3+CCR6+ Th1 and CD3+CD4+CXCR3CCR6+ Th17 cells, were higher in SLE than the HD. The proportions of CD19+CD20IgD+CD27+ central memory B cells and CD19+CD20IgD+CD27+ effector B cells were higher in SLE. The largest difference relative to the HD was observed in the proportion of CD19+CD20+IgD-CD27- effector B cells were higher in SLE.

Conclusions The proportions of CD19+CD20+IgD-CD27- effector B cells were higher in SLE.

Background and aims Tregs from SLE patients showed a significantly reduced number, elevated apoptosis rates and impaired suppressive capacity compared with NCs. The largest difference relative to the HD was observed in the proportion of CD19+CD20-CD27+CD38+ plasmablasts, which was higher in SLE than the HD. The proportions of CD19+CD20+IgD-CD27- effector B cells were higher in SLE.

Conclusions This global picture of pathway-specific expression signatures is a step further dissecting Treg cell defects in the pathogenesis of SLE, and may shed light on the newly therapeutic strategies towards the aberrant Treg apoptosis and reconstruction of SLE immune homeostasis.