World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:16, No:04, 2022

Transcriptional Differences in B cell Subpopulations over the Course of Preclinical Autoimmunity Development

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Abstract : Background: Systemic Lupus Erythematosus (SLE) is an interferon-related autoimmune disease characterized by B cell dysfunction. One of the main hallmarks is a loss of tolerance to self-antigens leading to increased levels of autoantibodies against nuclear components (ANAs). However, up to 20% of healthy ANA+ individuals will not develop clinical illness. SLE is more prevalent among women and minority populations (African, Asian American and Hispanics). Moreover, African Americans have a stronger interferon (IFN) signature and develop more severe symptoms. The exact mechanisms involved in ethnicity-dependent B cell dysregulation and the progression of autoimmune disease from ANA+ healthy individuals to clinical disease remains unclear. Methods: Peripheral blood mononuclear cells (PBMCs) from African (AA) and European American (EA) ANA- (n=12), ANA+ (n=12) and SLE (n=12) individuals were assessed by multimodal scRNA-Seq/CITE-Seq methods to examine differential gene signatures in specific B cell subsets. Library preparation was done with a 10X Genomics Chromium according to established protocols and sequenced on Illumina NextSeq. The data were further analyzed for distinct cluster identification and differential gene signatures in the Seurat package in R and pathways analysis was performed using Ingenuity Pathways Analysis (IPA). Results: Comparing all subjects, 14 distinct B cell clusters were identified using a community detection algorithm and visualized with Uniform Manifold Approximation Projection (UMAP). The proportion of each of those clusters varied by disease status and ethnicity. Transitional B cells trended higher in ANA+ healthy individuals, especially in AA. Ribonucleoprotein high population (HNRNPH1 elevated, heterogeneous nuclear ribonucleoprotein, RNP-Hi) of proliferating Naïve B cells were more prevalent in SLE patients, specifically in EA. Interferon-induced protein high population (IFIT-Hi) of Naive B cells are increased in EA ANA- individuals. The proportion of memory B cells and plasma cells clusters tend to be expanded in SLE patients. As anticipated, we observed a higher signature of cytokine-related pathways, especially interferon, in SLE individuals. Pathway analysis among AA individuals revealed an NRF2-mediated Oxidative Stress response signature in the transitional B cell cluster, not seen in EA individuals. TNFR1/2 and Sirtuin Signaling pathway genes were higher in AA IFIT-Hi Naive B cells, whereas they were not detected in EA individuals. Interferon signaling was observed in B cells in both ethnicities. Oxidative phosphorylation was found in age-related B cells (ABCs) for both ethnicities, whereas Death Receptor Signaling was found only in EA patients in these cells. Interferon-related transcription factors were elevated in ABCs and IFIT-Hi Naive B cells in SLE subjects of both ethnicities. Conclusions: ANA+ healthy individuals have altered gene expression pathways in B cells that might drive apoptosis and subsequent clinical autoimmune pathogenesis. Increases in certain regulatory pathways may delay progression to SLE. Further, AA individuals have more elevated activation pathways that may make them more susceptible to SLE.

Keywords :
Conference Title : ICCIDT 2022 : International Conference on Clinical Immunology and Disease Therapies
Conference Location : Venice, Italy
Conference Dates : April 14-15, 2022