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"Impaired expansion and selection of geminal center B cells drives disease progression in lupus"

by
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Molecular Biology, Genetics, and Cancer Program

B.Sc., 2017, Stony Brook University, Stony Brook, NY

Thesis Advisor: Jason Weinstein, Ph.D.
Department of Medicine

Tuesday, June 13th, 2023
10:00 AM
Cancer Center, G1196

Join Zoom Presentation:
https://rutgers.zoom.us/j/98805938609?pwd=YzBob0plaGo2UitYYWgzelVFc2Vsdz09

Meeting ID: 988 0593 8609
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ABSTRACT

Systemic lupus erythematosus (SLE, lupus) is an autoimmune disease characterized by the generation of autoantibodies that form immune complexes that deposit in tissues, leading to inflammation and organ damage. The origin of autoantibodies is not clear, but pathogenic autoantibody-secreting B cells in lupus undergo affinity maturation and differentiation in germinal centers (GCs) within secondary lymphoid organs. In lupus, there is a breakdown in selection as B cells that enter the GC as non-autoreactive ultimately leave as autoreactive B cells. Yet, the dysregulation in GCs leading to the generation of these autoreactive B cells and how it impacts their propagation in lupus remains unclear. Within the GC, B cells cycle between two microanatomical regions: the dark zone (DZ) where mutation and proliferation occur, and the light zone (LZ) where affinity-based selection occurs. Cells cycle between these two zones based on the strength of selective signals, including CD40 and IL-21R which work together to induce MYC. This zonal recycling generates high-affinity B cells that will differentiate and exit the GC as memory B cells or long-lived plasma cells. Using lupus-prone mouse models, we show that as autoantibody titers increased, DZ B cells decreased over disease progression while LZ B cells that should be whittled down by selection are instead increased. We found that this accumulation in the LZ was not due to hyperproliferation of the DZ compartment. Furthermore, we found no change in the rate of apoptosis of DZ or LZ B cells, suggesting that instead of dying by failed selection, LZ B cells remain and may erroneously differentiate into autoantibody-secreting cells by permissive selection. This failure in selection was further demonstrated by a reduction in the transcription factor MYC and a loss of BCR diversity and mutational burden as disease progressed, all in conjunction with the onset of the disease phenotype. Furthermore, we found that while there was an accumulation of LZ B cells, there was an increase in the generation of plasma cells, suggesting aberrant selection and differentiation into these potentially autoantibody-secreting cells. Thus, our findings identified a dysregulation in LZ B cell signal transduction that leads to permissive selection of autoreactive B cells, resulting in their differentiation into autoantibody-secreting cells and exacerbating disease pathology.