2023 Annual Research Day Poster Sessions – April 19th, 2023

Session/Poster#	Presenter
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Effects of Hydroxychloroquine on B cell tolerance in the germinal center

Rationale: Systemic lupus erythematous is an autoimmune disease mediated by antinuclear antibodies. Hydroxychloroquine (HCQ) has been used for nearly 60 years as the first-line lupus treatment. HCQ prevents flares by suppressing lupus autoimmunity but sparing normal immune functions. However, HCQ's mechanism remains unclear. We hypothesize that HCQ enhances the protective B cell tolerance regulated by sphingomyelin synthase 2 (SMS2) in the germinal center (GC). We reported that SMS2 prevents lupus in mice by activating pro-apoptotic activity of PKCÎ´ in autoreactive GC B cells. An antitumor drug 2OHOA can alleviate lupus pathogenesis in NZBWF1 mice, a preclinical lupus model, by activating the SMS2/PKCÎ´ pathway. As HCQ has been reported to increase SM synthesis, it is reasonable to test whether HCQ works via activating SMS2/PKCÎ´ tolerance pathway in GC B cells.
Methods: Proteinuria and serum anti-dsDNA IgGs in mice were assessed by Bradford Assay and ELISA respectively. NZBWF1 mice received HCQ (16mg/kg/day) or 2OHOA (400mg/kg/day) by oral gavage for 4 weeks when their serum anti-dsDNA IgG level reached 3ug/ml. Control mice were treated with an empty vehicle. Splenocytes were isolated for flow cytometry and mass spectrometer analysis.
Results: 2OHOA and HCQ treatments both reduced GC B cells and similarly changed GC B cells' lipidomic profile. Although HCQ treatment can reduce proteinurea, serum anti-dsDNA IgG levels was not significantly reduced. Thus, HCQ seems capable of activating SMS2-regulated tolerance in GC B cells. This conclusion, however, needs to be confirmed by further studies.
Significance: The build-up of HCQ in the body causes adverse effects, forcing patients to discontinue the drug, resulting in flares. Understanding the mechanism of HCQ will help develop a new strategy to inhibit lupus autoimmunity with reduced HCQ usage. Therefore, this project has the potential to reduce the disease burden and disparities associated with lupus.