INHIBITION OF EZH2 AMELIORATES LUPUS-LIKE DISEASE IN MRL/LPR MICE

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Background: We previously revealed a role for EZH2 in inducing pro-inflammatory epithelial gene changes in lupus CD4+ T cells. Objectives: In this study, we sought to determine if inhibiting EZH2 ameliorates lupus-like disease in MRL/Lpr mice.

Methods: EZH2 expression levels in multiple cell types in lupus patients were evaluated using flow cytometry and mRNA expression data. Inhibition of EZH2 in MRL/lpr mice was achieved by DZNep intraperitoneal administration using a preventative and a therapeutic treatment model. Effects of DZNep on animal survival, anti-dsDNA antibody production, proteinuria, renal histopathology, cytokine production, and T and B cell numbers and percentages were assessed.

Results: EZH2 expression levels were increased in whole blood, neutrophils, monocytes, B cells, and CD4+ T cells in lupus patients. In MRL/lpr mice, inhibiting EZH2 with DZNep treatment before or after disease onset improved survival and significantly reduced anti-dsDNA antibody production. DZNep-treated mice displayed a significant reduction in renal involvement, splenomegaly, and lymphopenopathy. Lymphoproliferation and numbers of double-negative T cells were significantly reduced in DZNep treated mice. Concentrations of circulating cytokines and chemokines, including TNF, IFN-γ, CCL2, RANTES/CCL5, IL-10, KC/CXCL1, IL-12, IL-12p40 and MIP-1α/CCL4 were decreased in DZNep treated mice. Conclusion: EZH2 is upregulated in multiple cell types in lupus patients. Therapeutic inhibition of EZH2 ameliorates lupus-like disease in MRL/lpr mice, suggesting that EZH2 inhibitors may be repurposed as a novel therapeutic option in lupus patients.

Disclosure of Interests: None declared