Abstract Type: Poster
Presentation No.: PGN 030

TonEBP regulates antigen presentation, T cell differentiation and phagocytic activity of macrophages in pristane-induced lupus nephritis

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Objectives: Lupus nephritis is a serious complication of systemic lupus erythematosus (SLE) which is linked to the failure of clearing injured cells by phagocytosis, activation of antigen presenting cells, and loss of immune tolerance. Since macrophages have been implicated in the pathogenesis of SLE and TonEBP is a key regulator of macrophages, we aimed to identify the function of TonEBP in lupus nephritis.

Methods: We examined the role of TonEBP using a mouse model of SLE which was produced by an intraperitoneal injection of a tetramethylpentadecane named pristane. Mice with TonEBP haplo-deficiency, and myeloid-specific TonEBP deletion were used. In addition, Peritoneal macrophages from the TonEBP deficient mice were isolated for in vitro experiments.

Results: 8 months after pristane administration, hypertrophy of spleen and kidney, albuminuria, and mesangial matrix expansion were all ameliorated in TonEBP haplo-deficient animals indicating that TonEBP was involved in the pathogenesis of SLE. In order to investigate the role of macrophage TonEBP, we examined a line of mouse with myeloid-specific deletion of the TonEBP gene. We found that the increase in the number of Th1 and Th17 cells in response to pristane treatment was blocked in association with elevated number of Treg cells in the animals with myeloid-specific TonEBP deficiency. In addition, peritoneal macrophages from the TonEBP deficient mice displayed reduced expression of antigen presenting molecules while exhibiting elevated phagocytic activity.

Conclusions: These data demonstrate that TonEBP in macrophages plays a critical role in the pathogenesis of SLE by stimulation of antigen-presentation, suppression of phagocytosis, suppression of Treg cell development, and stimulation of Th1 and Th17 cell development.