KSN 2020
FULLY VIRTUAL MEETING

Abstract Type : Poster
Abstract Submission No. : PO-1048

Leukocyte Adhesion protein LFA-1 is required for induction of glomerulonephritis by MPO-ANCA in mice

Shenju Gou, Yanglin Hu, Peiqi Hu, Hong Xiao, Ronald Falk, Charles Jennette
Department of Pathology and Lab Medicine, University of North Carolina, United States

Objectives: Neutrophils play a critical role in the pathogenesis of anti-neutrophil cytoplasmic autoantibodies (ANCA) associated necrotizing crescentic glomerulonephritis (NCGN). β2-integrin–mediated neutrophil adhesion to endothelium is required for the development of ANCA-CGN. Lymphocyte function-associated antigen-1 (LFA-1) is a member of the β2-integrin family that is highly expressed on neutrophils and mediates neutrophil-endothelial interaction via interactions with endothelial intercellular adhesion molecule-1 (ICAM-1). However, the role of LFA-1 in ANCA-CGN is not clearly elucidated. In this study, we investigated the role of LFA-1 in murine anti-MPO induced NCGN.

Methods: Anti-MPO IgG was purified from the sera of MPO-/- mice immunized with murine MPO. Mice with knock out (KO) of LFA-1, and normal wild-type C57BL/6j mice (WT B6) were injected i.v. with 50ug/g body weight anti-MPO IgG. Circulating anti-MPO IgG was monitored by ELISA. Proteinuria, hematuria and leukocyturia were monitored, and mice were sacrificed at day 6 and kidney tissue obtained for pathologic examination. Neutrophil function was assayed *in vitro*.

Results: At day 6, WTB6 (n=8) and LFA-1 KO (n=9) mice that received anti-MPO IgG showed similar levels of circulating anti-MPO. All WT B6 mice developed hematuria and NCGN with mean 13.9% glomeruli with crescents and 6.3% necrosis. In contrast, LFA-1 KO mice had normal urine and substantially reduced NCGN with mean 0.9% crescents ($p<0.001$) and no necrosis ($p=0.001$). *In vitro* neutrophil function assay showed that anti-MPO IgG caused similar activation of neutrophils from LFA-1 KO and WT mice, *demonstrating* that LFA-1 deficiency does not influence neutrophil activation by anti-MPO.

Conclusions: Depletion of LFA-1 abrogates anti-MPO induced NCGN, demonstrating that LFA-1 is required in the pathogenesis of NCGN induced by anti-MPO antibodies by limiting recruitment but not by blocking activation of neutrophils. Pharmacologic blockade of LFA-1 may have a therapeutic role in ANCA disease.