THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-0275

Protective roles of proximal tubular Sirt6 in resiquimod-induced murine lupus nephritis model

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Objectives : Lupus nephritis is an autoimmune complex glomerulonephritis that develops as a complication of SLE. Dysregulation of intrarenal immune tolerance to nuclear autoantigens produces autoantibody and immune disorders. Sirt6 is the NAD^+-dependent deacetylase and mono-ADP ribosyltransferase and is involved in genome maintenance and metabolism. This study investigates the effect of proximal tubule-specific Sirt6 knockdown on murine lupus nephritis.
Methods : To investigate the role of Sirt6 specifically in proximal renal tubules, we crossed gGt1-cre mice and Sirt6flox/flox mice to generate Sirt6 conditional knock-out mice. The back area's skin was shaved and treated topically three times per week, with 100 μg of resiquimod in 100 μl of acetone for eight weeks. After murine kidney sample collection, we evaluated renal histology and immunofluorescent study for inflammatory cells and lymphatic vessels. We also evaluated inflammatory cytokines and chemokines, lymphangiogenic factors by qRT-PCR.
Results : The loss of Sirt6 in proximal tubules aggravates glomerular mesangial cell proliferation and tubulointerstitial inflammation, and there also increases glomerular deposition of IgG, IgM, and C3 in immunofluorescence staining. LYVE-1(+) lymphatic vessels have increased expression and infiltration of F4/80, CD11c, and B220 (+) inflammatory cells in proximal tubule-specific Sirt6 knock-out mice. The pro-inflammatory cytokines and chemokines such as ICAM-1, VCAM-1, MCP-1, BAFF, LTβ, and CXCL13 mRNA levels were increased compared with wild-type mice.
Conclusions : Our data suggest that proximal tubule Sirt6 is important in resiquimod-induced lupus nephritis, especially in regulating tubulointerstitial inflammation.