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Inhibition of VEGF-C/VEGFR-3 signaling pathway decrease lymphangiogenesis and tertiary lymphoid organ formation by regulation of TLR7/MyD88/IFN-α expression in lupus nephritis model

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Objectives : Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune-complex deposits and inflammatory cell infiltrations in multiple organs. Approximately half of lupus patients have nephritis. Lymphangiogenesis is the proliferation of lymphatic vessels (LVs), which regulate tissue fluid homeostasis and immune cell trafficking, responding to the tissue environment. In this study, we evaluated whether the inhibition of VEGF-C/VEGFR-3 signaling pathway improves lupus nephritis model.
Methods : For animal experiments, 7- to 8-week-old male BALB/c mice were used. For the induction of a lupus-like model, the dorsal skin of mice was shaved and given topical treatment every other day with 100 μg resiquimod dissolved in 100 μL acetone during the 8-week treatment. We had renal histology and immunofluorescent study for inflammatory cells and lymphatic vessels. We also had a qRT-PCR and Western blot analysis to evaluate inflammatory cytokines and chemokines, lymphangiogenic factors, and TLR7/type I IFN response.
Results : Inhibition of VEGF-C/VEGFR-3 signaling pathway by oral SAR131675 treatment (100mg/kg) decreased the resiquidmod-induced glomerular injury and attenuated LYVE-1 and VEGFR-3 (+) lymphatic vessel expression and TLOs formation in the murine lupus model. SAR131675 treatment decreased the resiquimod-induced increase of lymphangiogenic factors, proinflammatory cytokines and chemokine by regulating TLR7/MyD88/IFN-α expression.
Conclusions : This study suggests the therapeutic potential of targeting lymphatic proliferation by the inhibition of VEGF-C/VEGFR-3 signaling pathway in lupus nephritis. Modulation of the lymphatic network may provide a novel approach to treating chronic inflammation and attenuating renal autoimmune response.