

Pediatric Rheumatology Symposium 2017

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Kv1.3 Expression on Urinary Leukocytes in Lupus Nephritis: Potential for Targeted Immunotherapy

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Background: Lymphocyte activation depends upon a calcium signaling cascade that is regulated by voltage-gated potassium channels. Effector memory T cells (T_{EM}), which are implicated in the immunopathogenesis of a panel of autoimmune diseases, express the potassium channel Kv1.3. Dalazatide is a potent peptide inhibitor of the Kv1.3 channel that has shown potential efficacy in a Phase 1b plaque psoriasis trial. That inflammatory cytokine producing T_{EM} cells have been implicated in the pathogenesis of lupus nephritis suggests that targeting Kv1.3 may be a successful strategy in lupus nephritis as well.

Methods: Urinary cells were isolated from patients with systemic lupus erythematosus (SLE). Immunofluorescence was performed to quantify and characterize cells expressing Kv1.3. Peripheral blood T lymphocyte subsets were assayed *ex vivo* for Kv1.3 expression by flow cytometry. The effect of dalazatide on phorbol myristate acetate (PMA)/ionomycin-induced inflammatory cytokine expression by T_{EM} cells was evaluated by intracellular cytokine staining.

Results: In the urine, cells expressing Kv1.3 were found in every subject studied. Kv1.3 expression was detected on CD3+ lymphocytes in 13 of 13 samples studied (mean of 52% of ,range 10-100%). In 4 of 6 samples, Kv1.3 was detected on CD20+ B lymphocytes (mean 35%, range 0-100%), and CD14+ monocytes/macrophages (mean 50%, range 0-100%).

In the blood, Kv1.3 expression by CD8⁺ T_{EM} cells was significantly higher in patients with active lupus nephritis when compared to patients with inactive SLE or healthy controls. Dalazatide inhibited IFN- γ , IL-17 and TNF- α production by both CD4⁺ and CD8⁺ T_{EM} cells from SLE patients in a dose-dependent manner. Higher levels of dalazatide-mediated inhibition were observed in IFN- γ and TNF- α -expressing CD4⁺ T_{EM} cells from patients with active SLE when compared to samples from SLE patients with inactive disease.

Conclusions: Kv1.3 is detectable on urinary B lymphocytes, T lymphocytes, and macrophage, implying that inflammatory cells in the kidney may be targeted by this channel. Peripheral blood cell expression and functional data suggest that SLE T cells are more susceptible to inhibition by dalazatide than healthy T cells.