Modulation of lymphocyte potassium channel K_V1.3 by membrane-penetrating, joint-targeting immunomodulatory plant defensin

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We describe a cysteine-rich, membrane-penetrating, joint-targeting and remarkably stable peptide, EgK5, that modulates voltage-gated K_V1.3 potassium channels in T lymphocytes by a distinctive mechanism. EgK5 enters plasma membranes and binds to K_V1.3, causing current run-down by a phosphatidylinositol 4,5-bisphosphate-dependent mechanism. EgK5 exhibits selectivity for K_V1.3 over other channels, receptors, transporters and enzymes. EgK5 suppresses antigen-triggered proliferation of effector memory T cells, a subset enriched amongst pathogenic autoreactive T cells in autoimmune disease. PET-CT imaging with ^{18}F-labeled EgK5 shows accumulation of the peptide in large and small joints of rodents. In keeping with its arthrotropism, EgK5 treats disease in a rat model of rheumatoid dermatitis. It was also effective in treating disease in a rat model of atopic dermatitis. No signs of toxicity were observed at 10-100 times the *in vivo* dose. EgK5 shows promise for clinical development as a therapeutic for autoimmune diseases.