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Molecular Mechanism Underlying Enhancement of IL-10 Production by K^+ Channel Inhibition in Regulatory T Cells

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Summary

The intermediate-conductance Ca^{2+}-activated K^+ channel $K_{Ca}3.1$ is one of major K^+ channels expressing in T cells. $K_{Ca}3.1$ activation-induced hyperpolarization increases Ca^{2+} influx through voltage-independent Ca^{2+} channels, and generally promotes cell proliferation, differentiation, and cytokine production. The present study showed that $K_{Ca}3.1$ activators significantly suppressed anti-inflammatory cytokine IL-10 transcription in human T-cell lymphoma HuT-78 cells. IL-10 transcription was significantly inhibited by treatment with $K_{Ca}3.1$ activators (DCEBIO and SKA-31), and IL-10 reduction was almost completely recovered by co-treatment with 1 μM TRAM-34, a selective $K_{Ca}3.1$ blocker. $K_{Ca}3.1$ activator-induced repression of IL-10 transcripts was disappeared by pre-treatment with the calmodulin kinase II (CaMKII) inhibitor, KN-62. Significant changes in the protein expression ratio, Phosphorylated Smad2 (P-Smad2)/total Smad2 by treatments with $K_{Ca}3.1$ activators were found in Western blotting. Concomitant with the results from Western blotting, nuclear translocation of P-Smad2 was significantly inhibited by $K_{Ca}3.1$ activators. These suggest that $K_{Ca}3.1$ activators may repress IL-10 transcription through activation of CaMKII and subsequent prevention of nuclear translocation of P-Smad2 in IL-10-producing T cells. The transcriptional factors of IL-10, E4BP4, Blimp-1, and cMAF did not change their transcriptional expression by treatment with $K_{Ca}3.1$ activators. Our results describe a mechanism for $K_{Ca}3.1$-induced negative regulation of IL-10 through Smad signaling pathway. Activation of $K_{Ca}3.1$ inhibited the translocation of phospho-Smad2. $K_{Ca}3.1$ activators are a possible therapeutic option to suppress tumor promoting activities of IL-10.