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Physiological Role of the Two-Pore Domain K^+ Channel $K_{2P}5.1$ in T Cells and Novel Strategy to Regulate $K_{2P}5.1$ Activity by Pre-mRNA Splicing Inhibition

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Summary

The two-pore domain K^+ channel $K_{2P}5.1$ is as a possible therapeutic target for autoimmune and inflammatory disorders and cancers. $K_{2P}5.1$ K^+ channel plays an important role in regulation of Ca^{2+} signaling in T lymphocytes and cancer cells. However, the lack of selective $K_{2P}5.1$ blockers has led to difficulties conducting experimental studies on $K_{2P}5.1$ K^+ channel. First, we elucidate the pathological significance of the $K_{2P}5.1$ K^+ channel in inflammatory bowel disease (IBD). Significant levels of increase in both expression and activity of $K_{2P}5.1$ K^+ channel were observed in the $CD4^+$ T cells of the IBD model. The knockout of $K_{2P}5.1$ in mice significantly suppressed the disease severity in the IBD model. These suggest that dysregulated $K_{2P}5.1$ K^+ channel may stimulate the Th1 imbalance in IBD, and provide evidence for $K_{2P}5.1$ K^+ channel as a potential therapeutic target for IBD. Second, we identified an N-terminus-lacking, novel splicing isoform of $K_{2P}5.1$ K^+ channel, $K_{2P}5.1B$ from the human lymphoid tissues. In a heterologous expression system, $K_{2P}5.1B$ inhibited the plasma membrane trafficking of $K_{2P}5.1A$. The $K_{2P}5.1$ activity was significantly suppressed by $K_{2P}5.1B$-overexpression in human leukemia K562 cells, resulting in the prevention of cell viability. A pre-mRNA splicing inhibitor, pladienolide B significantly enhanced the expression levels of $K_{2P}5.1B$ without changes in those of $K_{2P}5.1A$ in K562 cells, resulting in decreases in the $K_{2P}5.1$ activity. These suggest that the pre-mRNA splicing mechanism underlying the posttranscriptional regulation of $K_{2P}5.1$ K^+ channel may be a new therapeutic strategy for inflammatory disorder and cancers. The target-oriented development of pre-mRNA splicing inhibitors is expected as a novel strategy of drug development for $K_{2P}5.1$ K^+ channel