Physiological Role of the Two-Pore Domain K⁺ Channel K₂p5.1 in T Cells and Novel Strategy to Regulate K₂p5.1 Activity by Pre-mRNA Splicing Inhibition

Susumu Ohya, Hiroaki Kito
Kyoto Pharmaceutical University

Summary

The two-pore domain K⁺ channel K₂p5.1 is a possible therapeutic target for autoimmune and inflammatory disorders and cancers. K₂p5.1 K⁺ channel plays an important role in regulation of Ca²⁺ signaling in T lymphocytes and cancer cells. However, the lack of selective K₂p5.1 blockers has led to difficulties conducting experimental studies on K₂p5.1 K⁺ channel. First, we elucidate the pathological significance of the K₂p5.1 K⁺ channel in inflammatory bowel disease (IBD). Significant levels of increase in both expression and activity of K₂p5.1 K⁺ channel were observed in the CD4⁺ T cells of the IBD model. The knockout of K₂p5.1 in mice significantly suppressed the disease severity in the IBD model. These suggest that dysregulated K₂p5.1 K⁺ channel may stimulate the Th1 imbalance in IBD, and provide evidence for K₂p5.1 K⁺ channel as a potential therapeutic target for IBD. Second, we identified an N-terminus-lacking, novel splicing isoform of K₂p5.1 K⁺ channel, K₂p5.1B from the human lymphoid tissues. In a heterologous expression system, K₂p5.1B inhibited the plasma membrane trafficking of K₂p5.1A. The K₂p5.1 activity was significantly suppressed by K₂p5.1B-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 K₂p5.1B without changes in those of K₂p5.1A in K562 cells, resulting in decreases in the K₂p5.1 activity. These suggest that the pre-mRNA splicing mechanism underlying the posttranscriptional regulation of K₂p5.1 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 K₂p5.1 K⁺ channel.