EDITORIAL

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Ca^{2+}-Activated K^+ Channel $K_{Ca}3.1$ as a Double-Edged Sword in the Treatment of Inflammatory Bowel Disease

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Inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic intestinal inflammation with abdominal symptoms, such as diarrhea, bloody stools, pain, and vomiting. Since chronic intestinal inflammation arises from abnormal responses of the innate and adaptative immune system, studies have been focused on immune system-mediated mechanisms. Anti-inflammatory drugs and monoclonal antibodies targeting pro-inflammatory cytokines are successful treatment in improvement of IBD symptoms. Apart from that, the epithelial barrier function is essential to the maintenance of intestinal homeostasis. Recent studies have indicated that a defective epithelial barrier by homeostatic dysfunction of the intestinal epithelial cell (IEC) leaded to IBD symptoms such as diarrhea and intestine ulcers [1].

Over 90 different K^+ channel genes have been identified in the mammalian genome. Ca^{2+}-activated K+ (K_{Ca}) channels are classified into large-conductance $K_{Ca}1.1$, small-conductance $K_{Ca}2.x$, and intermediate-conductance $K_{Ca}3.1$. For fine-tuning Ca^{2+} signaling, K_{Ca} channels are associated with voltage-gated and non-voltage-gated Ca^{2+} channels as complexes in excitable and non-excitable cells [2]. $K_{Ca}3.1$ encoded by *KCNN4* gene is also known as IK1, SK4, and IKCa1. In non-excitable cells such as immune cells, the activation of $K_{Ca}3.1$ promotes Ca^{2+} signaling by increasing the electrical driving force for Ca^{2+} entry through non-voltage-gated Ca^{2+} channels [3]. Genetic silencing and pharmacological inhibition of $K_{Ca}3.1$ have exhibited significant efficacy to suppress IBD symptoms by reducing inflammatory cytokine production from T cells in two different IBD model mice [4, 5]. Therefore, $K_{Ca}3.1$ is an attractive therapeutic target for autoimmune diseases including IBD, multiple sclerosis, and rheumatoid arthritis [6].

In IECs, $K_{Ca}3.1$ is a dominant basolateral K^+ channel, and K^+ efflux through $K_{Ca}3.1$ provides the driving force for Cl^- secretion in association with fluid secretion [7, 8]. Therefore, $K_{Ca}3.1$ inhibition leads to a reduction in water content in the stools. $K_{Ca}3.1$ regulates intestine function by controlling Cl^- secretion and water/salt balance. In the active stage of UC, a decrease in basolateral $K_{Ca}3.1$ expression and activity depolarizes the epithelial cell membrane potential and thereby suppresses the electrical driving force for electrogenic Na^+ transport. Consequently, it results in impaired Cl^- and water absorption across the inflamed mucosa [9, 10]. $K_{Ca}3.1$ channel opener enhances the Cl^- secretion in colonic epithelial cells through the cystic fibrosis transmembrane regulator (CFTR) and Ca^{2+}-activated Cl^- channel (TMEM16A/ANO1).

In the previous study, Wölfel's research group reported the involvement of $K_{Ca}3.1$ in epithelial ion transport and intestinal restitution [11]. They indicated that the expression levels of $K_{Ca}3.1$ transcript were high in IECs from IBD patients and that IEC migration was differentially regulated by $K_{Ca}3.1$ via the phosphoinositide 3-kinase (PI3K) signaling cascade. Their findings provided interesting insights into epithelial barrier dysfunction in chronic intestinal inflammation.

In this issue of the journal, Süss et al. [12] compared surgical samples from patients with IBD and uninflamed controls to determine the potential role of $K_{Ca}3.1$ as a diagnostic marker and/or therapeutic target. They showed the expression levels of $K_{Ca}3.1$ transcript and protein were elevated in IECs from CD and UC patients. Notably, in monolayers of IEC-18 cells pretreated with IFN-γ, FITC dextran efflux assay that is used as an index of transepithelial permeability unraveled that $K_{Ca}3.1$ openers stabilized epithelial barrier function *in vitro* by improving epithelial monolayer integrity. These suggest that $K_{Ca}3.1$ may have a protective role in the epithelial barrier in IBD. They concluded that $K_{Ca}3.1$ might serve a protective role in IBD and might be a novel target for IBD diagnosis and

treatment due to the beneficial effects of $K_{Ca}3.1$ openers on epithelial restitution.

The following compounds are well-known as potent $K_{Ca}3.1$ activators: 1-EBIO (1-ethylbenzimidazolin-2-one), DCEBIO (5,6-dichloro-1-ethyl-1,3-dihydro-2H-benzimidazol-2-one), NS309 (6,7-dichloro-1H-indole-2,3-dione 3-oxime), and SKA-31 (naphtho[1,2-d]thiazol-2-ylamine). In this issue, 1-EBIO and SKA-31 were used as $K_{Ca}3.1$ openers; however, they exhibit similar potency for small-conductance $K_{Ca}2.x$. Recently, the selective $K_{Ca}3.1$ activator SKA-121, a derivative of SKA-31, was developed using Rosetta modeling [13]. SKA-121 may have an effective therapeutic profile for chronic intestinal inflammation caused by defective epithelial barrier function in IBD.

$K_{Ca}3.1$ gene expression is positively and negatively regulated by transcriptional factors [activator protein-1 (AP-1) (Fos/Jun heterodimers) and repressor element-1 silencing transcription factor (REST)] and by epigenetic modifications (DNA methylation, histone acetylation, and RNA interference) [3, 14-16]. Indeed, histone deacetylase (HDAC) inhibitors suppressed intestinal inflammation in IBD [17]. Also, spliceosomal and proteasomal regulation contribute to the tuning of $K_{Ca}3.1$ activity [18-21]. Further investigations will clarify the molecular mechanisms underlying $K_{Ca}3.1$ upregulation in IECs of IBD patients.

Recent studies provided the potential involvement of gut microbiota alternation in the pathogenesis of IBD [22, 23]. Microbiota dysbiosis is profoundly associated with impaired epithelial barrier function in IBD [24]. IECs function as a coordinator between microbiota and the immune system, and aberrant balance of fluid and electrolyte absorption and secretion influence not only barrier function but also microbiota composition and mucosal immune homeostasis in the luminal microenvironment. A further understanding will be required to elucidate the role of $K_{Ca}3.1$ openers as therapeutic agents in the management of IBD in the improvement of barrier dysfunction-mediated microbiota dysbiosis.

A recent study showed that increased intracellular K^+ ($[K^+]i$) in tumor microenvironment reduced pro-inflammatory cytokine expression by inhibiting the AKT signaling pathway [25]. Therefore, the reduction of [K+]i by $K_{Ca}3.1$ openers may influence barrier function in IECs without changing the electrical driving force, and may, at least in part, be the enhancement of IEC proliferation and migration via the activation of PI3K/AKT signaling cascade.

In conclusion, Ca^{2+}-activated K^+ channel $K_{Ca}3.1$ is a double-edged sword in the inflammatory responses and impaired epithelial barrier function during the process of IBD development. $K_{Ca}3.1$ activation-induced rise of Ca^{2+} influx in inflammatory CD4+ T cells promotes pro-inflammatory cytokine expression and production. Additionally, $K_{Ca}3.1$ plays an important role in the maintenance of intestinal homeostasis, and upregulated $K_{Ca}3.1$ in IECs of IBD patients protects impaired epithelial barrier function in IBD. Therefore, $K_{Ca}3.1$ inhibitors preventing inflammatory responses and $K_{Ca}3.1$ openers repairing aberrant epithelial barrier function are both possible therapeutic potentials for IBD. Based on the recent advances in IBD research, the barrier function, immune system, and intestinal microbiome are tripartite circuit of IBD pathogenesis. Further investigations will elucidate the integrated roles of these three components in the active and remission stages of IBD.

Conflicts of interests: None to declare.

Authors' contribution: S.O. conceived and designed the editorial. S.O.,M.M. drafted the manuscript. S.O., M.M., J.K. critically revised the manuscript and approved the final version.

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