Post-transcriptional regulation of Ca^{2+} -activated K^+ channel $\text{K}_{\text{Ca}}3.1$ by histone deacetylase in CD4^+ cells of the inflammatory bowel disease model mice

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Background: The intermediate-conductance Ca^{2+} -activated K^+ channel ($\text{K}_{\text{Ca}}3.1$) is one of the key molecules that modulate Ca^{2+} signaling by controlling Ca^{2+} entry through Ca^{2+} release activated Ca^{2+} channels in T cell. Our previous study demonstrated that the up-regulation of $\text{K}_{\text{Ca}}3.1$ in CD4^+ T cells was involved in the pathogenesis of inflammatory bowel disease (IBD), and a significant decrease in IBD disease severity was elicited by administration of the $\text{K}_{\text{Ca}}3.1$ inhibitor, TRAM-34. $\text{K}_{\text{Ca}}3.1$ is possible therapeutic target for IBD, however, the mechanism of $\text{K}_{\text{Ca}}3.1$ up-regulation in CD4^+ T cells remains unclear. Recent studies showed that histone deacetylase inhibition *in vivo* decreases disease responses in IBD. We examined the involvement of HDACs in up-regulation of $\text{K}_{\text{Ca}}3.1$ in CD4^+ T cells from IBD model mice.

Methods: The mouse model of IBD was prepared by exposing male C57BL/6 mice to 5% dextran sulfate sodium for 7 days. Isolated splenocytes from IBD model mice were cultivated in the presence of the lectin, concanavalin A (Con A, 5 $\mu\text{g/mL}$) for 48 hr. 24 hours after the cultivation, cell suspensions were treated with vehicle control or HDAC inhibitors. CD4^+ T cells were then isolated using the Dynabeads technology. The expression levels of $\text{K}_{\text{Ca}}3.1$, HDACs, and $\text{K}_{\text{Ca}}3.1$ -related genes were determined by real-time PCR and/or western blot assays. $\text{K}_{\text{Ca}}3.1$ inhibitor-induced depolarization responses were monitored by voltage-sensitive dye imaging. All HDAC inhibitors were supplied by Professor Suzuki (Kyoto Prefectural University of Medicine, Japan).

Results: Real-time PCR assay showed the significant level expression of class I HDAC members (HDAC1, 2 and 3) in CD4^+ T cells of normal mice, and they were significantly up-regulated in IBD model. Several activator protein 1 (AP1) components that are possible regulators of $\text{K}_{\text{Ca}}3.1$ transcription also up-regulated in IBD model. The treatment with the pan-HDAC inhibitor vorinostat (1 μM) induced both down-regulation of $\text{K}_{\text{Ca}}3.1$ and decrease in $\text{K}_{\text{Ca}}3.1$ activity in CD4^+ T cells. Moreover, the selective inhibition of HDAC2 and HDAC3 significantly down-regulated $\text{K}_{\text{Ca}}3.1$.

Conclusion: These findings suggest that HDAC2/3 may be involved in the post-transcriptional regulation of $\text{K}_{\text{Ca}}3.1$ in inflammatory CD4^+ cells.