Contribution of voltage-gated cation channels to immunity: function and importance of localization within the membrane

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In this study we showed that $CD1a^+$ monocyte-derived immature dendritic cells (DC) express the voltage-gated Nav1.7 channel. We found that this voltage-gated sodium channel sets the membrane potential of these cells, thereby may modulate the threshold of dendritic cell activation, maturation. Inhibition of Nav1.7 channel by tetrodotoxin results in increased cytokine secretion of $CD1a^+$ immature dendritic cells (IDC) upon suboptimal cytokine cocktail stimulation, which suggests, that the channel has an important functional role during DC activation and differentiation. These facts confirmed our hypothesis that the presence of Nav1.7 channels in the plasma membrane of $CD1a^+$ IDC keeps the membrane potential at a "depolarized state" (app. -10 mV), thus protecting the cell from unnecessary or harmful activation below an actively set threshold. Since the transition of IDC to mature dendritic cells (MDC) is a crucial step in triggering both innate and adaptive immunity, these findings shed light to a new regulatory mechanism, by which DC functions may be controlled.

We also investigated the association of a voltage-gated potassium channel, Kv1.3, with two different scaffolding proteins in human T cells. We found that Kv1.3 interacts with both PSD-95 and SAP97, and this interaction occurs only through the C-terminal of the channel. Deleting this region of Kv1.3, or knocking down PSD-95 in a human T cell line significantly decreased the fraction of T cells displaying Kv1.3 accumulation at the immunological synapse upon T cell conjugation to an antigen presenting cell. On the other hand, SAP97 had no effect on Kv1.3 redistribution, implying that PSD-95 could be responsible for the rearrangement of the channel during the formation of this supramolecular cluster. The exact function of Kv1.3 channels at the immunological synapse is still not fully understood, however we believe that elucidation of the mechanisms by which these channels can be recruited to the IS may help us in resolving this issue.

In summary this work focused on two different immune cell types and their dominant voltage-gated ion channels, which are both crucial in triggering an adequate immune response to different stimuli. Understanding the appropriate function and regulation of these channels may bring us closer to discovering possible causes of, and even therapies for various immune diseases.

Keywords: ion channel, patch-clamp, dendritic cell, T cell, Nav1.7, Kv1.3, immunological synapse, MAGUK proteins

Kulcsszavak: ioncsatorna, patch-clamp, dendritikus sejt, T sejt, Nav1.7, Kv1.3, immunológiai szinapszis, MAGUK fehérjék