ABSTRACT

Early Morning Workshops

2-EW-01-1 The involvement of TRPM2 channel in insulin secretion and the development of diabetes

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The gene encoding the capsaicin receptor as a noxious heat sensor, which is now called TRPV1, was isolated from a rodent sensory neuron cDNA library in 1997 and was considered to be a breakthrough for research concerning temperature sensing. Since then, several TRP channels having thermosensitive ability have been identified in mammals, with ten thermosensitive TRP channels reported in mammals to date. While searching for a novel thermosensitive TRP channel, we found that TRPM2 has thermosensitivity, and its temperature-dependent activation is drastically enhanced by co-application of ligands such as cyclic adenosine 5-diphosphoribose (ADPR). Interestingly, TRPM2 is mainly expressed in the tissues not exposed to the drastic temperature changes. TRPM2 was originally cloned as the target of ADPR that cause intracellular Ca^{2+} increase, and has been reported to be activated by nicotinamide adenine dinucleotide, hydrogen peroxide and intracellular Ca^{2+}. In addition, TRPM2 has Ca^{2+}-permeability, indicating that its physiological roles might depend on intracellular Ca^{2+} increases. In this symposium, we would like to talk about the involvement of TRPM2 in insulin secretion and the development of diabetes.

2-EW-01-2 Activation of spinal microglia by P2X4 channels and chronic pain

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Injury to the nervous system results in causing a debilitating chronic pain state (neuropathic pain). Its underlying mechanisms remain unclear, and currently available treatments are frequently ineffective. It has long been considered that pathological hyperexcitability of dorsal horn neurons evoked by peripheral sensory inputs after peripheral nerve injury (PNI) occurs in a cell-autonomous fashion, but accumulating evidence has changed this view. I will show our findings indicating that spinal microglia activated by the purinergic receptor subtype P2X4 channels are necessary for the pathogenesis of neuropathic pain. PNI increases expression of P2X4 exclusively in spinal microglia in a manner that requires an IRF8-IRF5 transcriptional axis. P2X4 channels are activated by extracellular ATP released from dorsal horn neurons that involves the vesicular nucleotide transporter VNUT (a secretory vesicle protein responsible for the storage and release of ATP). Genetic knockout of these molecules results in reducing PNI-induced mechanical allodynia, a cardinal symptom of neuropathic pain. These findings provide new insight into the mechanisms for pain hypersensitivity after PNI and a new target for treating chronic pain.

2-EW-01-3 Pathophysiological roles of K^+ channels in inflammatory bowel disease

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Inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease afflicts more than 0.1% of the population worldwide. K^+ channels play important roles in the modulation of Ca^{2+} signaling in T cells. Our studies have showed up-regulation of the two different K^+ channel subtypes $K_{Ca}3.1$ and $K_{2P}5.1$ functionally expressing in inflammatory $CD4^+$ T cells of chemically-induced IBD model mice and improvement of IBD disease severities by pharmacological blockade of $K_{Ca}3.1$- or genetic inhibition of $K_{2P}5.1$-induced reduction of inflammatory cytokines. Of interest, in regulatory $CD4^+CD25^+$ T cells of semi-chronic IBD model mice, *in vivo* administration of a $K_{Ca}3.1$ blocker, TRMA-34 (1 mg/kg, s.c.) increased the anti-inflammatory cytokine IL-10 expression. Recently, we identified the N-terminus-lacking splice variants of $K_{2P}5.1$, which inhibited the $K_{2P}5.1$ trafficking to the plasma membrane and suppressed the channel activity in a dominant-negative manner. The pre-mRNA splicing inhibitor, pladienolide B markedly decreased full-length $K_{2P}5.1$ transcription in activated $CD4^+$ T cells, resulting in the disappearance of $K_{2P}5.1$ activity. These provided new insights on drug development focused on K^+ channel-dysregulated autoimmune and inflammatory diseases.

2-EW-02-1 Pathogenic roles of P2 receptors dysregulation in hypertensive glaucoma

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The glaucoma is an optic neuropathy characterized by progressive degeneration of retinal ganglion cells (RGCs) and is the first cause of leading blindness in Japan. An elevation of intraocular pressure (IOP) is one of the highest risks for pathogenesis of glaucoma. However, existing medications that decrease IOP are not sufficient for some patients. Therefore, new molecular targets have been desired. Here, we report that $P2Y_6$ receptor is a promising molecule for that. We found that topical application of uridine diphosphate (UDP), an endogenous $P2Y_6$ receptor agonist, reduces IOP. $P2Y_6$ receptor deficient ($P2Y_6$KO) mice showed significantly higher IOP and were insensitive to UDP. Aged but not young $P2Y_6$KO mice showed significant structural abnormalities in optic nerves assessed by serial block-face scanning electron microscopy. Corresponding this, the number of RGCs was decreased in an age-dependent fashion in the mutant mouse. Finally, multifocal electroretinogram showed that the aged but not young $P2Y_6$KO mice showed significant deficiencies in visual functions. Taken together, our data show that $P2Y_6$ receptor is essential for IOP lowering and its dysfunction causes hypertensive glaucoma-like optic neuropathy.

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