Structure and function of inositol 1,4,5-trisphosphate (IP_3) receptor and its cell function – from discovery to the new concept

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We started to work on IP_3 receptor as P400 protein missing in the two cerebellar mutant mice in 1977-1978 (Proceeding of Physiol Soc.1977) (Brain Res. 142 487-504 1978, Develop Neurosci.2 254-275 1979): one is the mutant where Purkinje neurons are absent and second one is the mutant where dendritic arborization of Purkinje neuron is poor and synapses are absent. Therefore we started to work on IP_3 receptor as P400 protein as a developmentally regulated glyco-phosphoprotein more than several years before IP_3 was found as a second messenger (Streb et al. Nature 1983). We first purified IP_3 receptor into homogeneity (J. Neurochem. 51 1724-1730 1988). Then we found that P400 is IP_3 receptor and determined the primary structure which was the second longest sequence at that time (Nature 342 32-38 1989). We found that IP_3 receptor is an IP_3 gated ion channel using purified IP_3 receptor in lipid bilayer (J. Biol. Chem. 266 1109-1116 1991). We first showed that the Ca^{2+} store is smooth endoplasmic reticulum (ER) by using specific antibody by electron microscopy (Cell Struct. Funct. 15 163-173 1990).

Therefore, IP_3 receptor is a signal converter from the IP_3 signal to Ca^{2+}. We could show that Ca^{2+} wave is produced through IP_3 receptor by using specific monoclonal antibody against type 1 IP_3 receptor in hamster egg. This is the first demonstration that IP_3 receptor works as a Ca^{2+} oscillator (Science 257 251-255 1992). Furthermore, we discovered that IP_3 is involved in determination of dorso-ventral axis formation at four cell stage after fertilization (Science 278 1940-1943 1997), and it is also important for neurite extenstion (Science 282 1705-1708 1998). We produced IP_3 receptor (type 1) deficient mice (Nature 379 168-171 1996) which showed epileptic seizure and cerebellar ataxia. We found by the analysis of the mutant mice that IP_3 receptor is important in neural plasticity, and determination of spine specificity (Nature 408 584-588 2000).

Biochemical study revealed that IP_3 receptor has a unique biochemical property as following; 1) even though IP_3 receptor is fragmented into several pieces by trypsin digestion, IP_3 binding activity and Ca^{2+} release activity is intact (J.Biol.Chem. 274 316-327, 328-334 1999) 2) IP_3 binding core has 1000 times higher affinity compared with native IP_3 receptor covered with inhibitory sequence at N-terminal (J.Biol.Chem.277 8106-8113 2002). X-ray 3-dimensional crystalographic analysis showed combined structure of _-domain (composed of _-helix) and _-domain (composed of _-sheet) (Nature 420 696-700 2002). 3) IP_3 receptor interacts with many molecules and moves dynamically inside the cell (J. Biol. Chem. 278 4048-4056 2003).
4) We discovered that IP_3 receptor releases novel molecule, IRBIT, upon IP_3 binding, presumably acting as a signaling molecule downstream of IP_3R (J.Biol.Chem. 278 1062-20612 2003). 5) Contrary to the traditional concept that ER (endoplasmic

reticulum) forms reticular structure, we discovered that ER vesicles carrying IP_3 receptor capable of Ca^{2+} uptake and release move rapidly along microtubules using kinesin motor.

IP_3 receptor is an IP_3 gated Ca^{2+} channel and works as a Ca^{2+} oscillator and plays a crucial role in variety of cell functions, which may be based on the above mentioned unique biochemical properties of the IP_3 receptor.