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Regulatory Mechanism of Calcium inside the Cell and Its Role in Physiological Function—Development of New Drugs for Therapeutic Uses for Its Abnormalities

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When cells are stimulated IP_3 is produced (inside the cell) and subsequently the intracellular Ca^{2+} concentration increases - the later initiates/modulates a plethora of diverse physiological responses. It is now known that the IP_3 receptor regulates Ca^{2+} release from the endoplasmic reticulum, a major intracellular Ca^{2+} store, and hence plays an important role in living systems. However despite its importance, the mechanism through which IP_3 increases intracellular Ca^{2+}concentration was still unknown. We identified the IP_3 target molecule and its role as a Ca^{2+} release channel. The work originated from an analysis of the protein P400 (now named the IP_3 receptor), which is greatly decreased in the cerebellum of ataxic mutant mice. We purified the P400 and the generated specific monoclonal antibodies against it. We found P400 as the IP_3 receptor. IP_3 receptor was shown to be located on the endoplasmic reticulum. We determined the entire sequence of the IP_3 receptor by cDNA cloning (1989).

We identified IP_3 receptor as an allosteric protein that changes its form (from windmill to square form) reversibly in the presence and absence of Ca^{2+}. We also succeeded in conducting a three dimensional crystallographic analysis of both the IP_3 binding core and the regulatory region of the IP_3 receptor, and from this clarified the IP_3 receptor pore gating mechanism.

We demonstrated that the IP_3 receptor is a Ca^{2+} oscillator and essential in: fertilization; dorso-ventral axis determination at the 4- to 8- cell stage after fertilization; cell division; and neurite extension. Furthermore IP_3 receptor type 1 deficient mice showed: cerebellar ataxia, demonstrating that the type 1 receptor is important for neuronal plasticity; an abnormal secretion of the nerve growth factor, BDNF. Comparatively, the analysis of IP_3 receptor type 2 and type 3 double deficient mice revealed an absence of exocrine function and a phenotype similar to that of Sjögren syndrome (which is characterized by dry eyes and dry mouth). Interestingly Sjögren syndrome patients were recently shown to have antibodies (in their blood) against the IP_3 receptors.

We recently discovered an endogenous pseudo IP_3, IRBIT (IP_3 receptor binding protein released with inositol 1,4,5-trisphosplate) that binds to the IP_3 binding core and is released following IP_3 application. IRBIT not only regulates the amplitude and frequency of Ca^{2+} oscillation, but also acts as a tertiary messenger - activating the Na^+HCO^- cotransporter 1 and thereby regulating the acid-base balance. To re-iterate this important new finding, the function of IP_3 is not only to release Ca^{2+} but also to regulate acid-base balance. Furthermore, redox (oxydo-reduction) regulation was considered to be independent of Ca^{2+} signaling, but we linked the two signaling systems by discovering ERp44 as a new redox sensor that regulates the IP_3 receptor. We have screened the proteins associated with the IP_3 receptor and identified various molecules such as 4.1N, TRP channel, and glutamate receptors. These findings suggest that the IP_3 receptor is closely linked with many other signaling pathways and various diseases. We have developed various drugs that can modulate the regulatory mechanism of Ca^{2+} signaling in side the cell, which will be contribute to be a therapeutic drugs for the diseases that may arise from the abnormality of the regulation mechanism.