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Dynamic regulation of calcium signalling

ER is the major intracellular calcium store from which receptors that stimulate formation of inositol 1,4,5-trisphosphate ($IP_3$) evoke calcium release via $IP_3$ receptors. The resulting increases in cytosolic calcium concentration are precisely organized in both time and space, and they regulate almost every cellular activity. ER is a dynamic organelle that forms intimate contacts with the plasma membrane and with every other intracellular organelle, including mitochondria, Golgi and lysosomes. The importance of spatially organized calcium signals suggests that dynamic regulation of intracellular organelles may be as important as the underlying biochemical pathways in defining the behaviour of signalling pathways. How do dynamic organelles contribute to delivery of intracellular messengers to $IP_3$ receptors and to shaping the calcium signals they evoke? We address these questions by simultaneously recording subcellular distributions of intracellular messengers and of the proteins and organelles that generate and decode them. This requires analysis of single molecules (eg, patch-clamp, microscopy, structural biology) and cells (eg, imaging, high-throughput analyses) using approaches that include super-resolution microscopy, TALEN-mediated gene-editing, electrophysiology, structural and molecular biology and collaborations with chemists, mathematicians and experts in NMR and crystallography. This project will use super-resolution optical microscopy with new intracellular indicators for $IP_3$ and calcium to examine the role of dynamic organelles in shaping $IP_3$-evoked calcium signals.

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