

Intracellular Calcium Signaling

Calcium regulates a wide range of vital cell functions including enzyme activities, attachment, motility, morphology, metabolic processes, cell-cycle progression, signal-transduction, replication, gene expression and electrochemical responses. The external concentrations of calcium are typically four orders of magnitude higher than internal levels. Signaling is activated by temporary increases in intracellular calcium concentration through the opening of calcium channels in the plasma membrane or the endoplasmic reticulum (ER). Prolonged elevation of intracellular calcium levels can lead to apoptosis.

Calcium is stored in the endoplasmic reticulum (ER). Proteins that bind calcium within the ER lumen include protein disulfide isomerase, calreticulin, endoplasmin and reticulocalbin. Calcium acts as a diffusible second messenger when it is released from the endoplasmic reticulum by inositol-3-phosphate (IP3), a metabolite of the cleavage of phosphatidylinositol 4,5 biphosphate (PIP2) by members of the PI-phospholipase C family of enzymes. Phospholipase C enzymes are differentially activated directly and indirectly by a wide variety of cell surface receptors including growth factors, cytokines, G-protein coupled receptors (GPCR) and integrins. Calcium mediates its affect on cellular activities and signaling cascades by binding to a variety of proteins including, but not limited to, calbindins, troponin C, S-100, calmodulin and calcineurin.

The ubiquitous, calcium-binding protein calmodulin (CaM) mediates a wide range of cellular processes. Calcium activated calmodulin (Ca^{2+} -CaM) can activate calmodulin kinase kinase (CaMKK), which is an activator of CaM kinases, I and IV. CaMKK can phosphorylate protein kinase B (PKB) and inhibit apoptosis. Ca^{2+} -CaM influences the level of cyclic nucleotides by regulating the activity of cyclic nucleotide phosphodiesterase (PDE1) isozymes. Protein phosphatase 2B (PP2B), calcineurin (CN), is expressed in many tissue and affects a variety of cell processes such as gene transcription. For example, it dephosphorylates the transcription factor NFAT in the cytoplasm consequently allowing it to enter the nucleus where it upregulates IL-2 synthesis.

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