Intracellular calcium signaling

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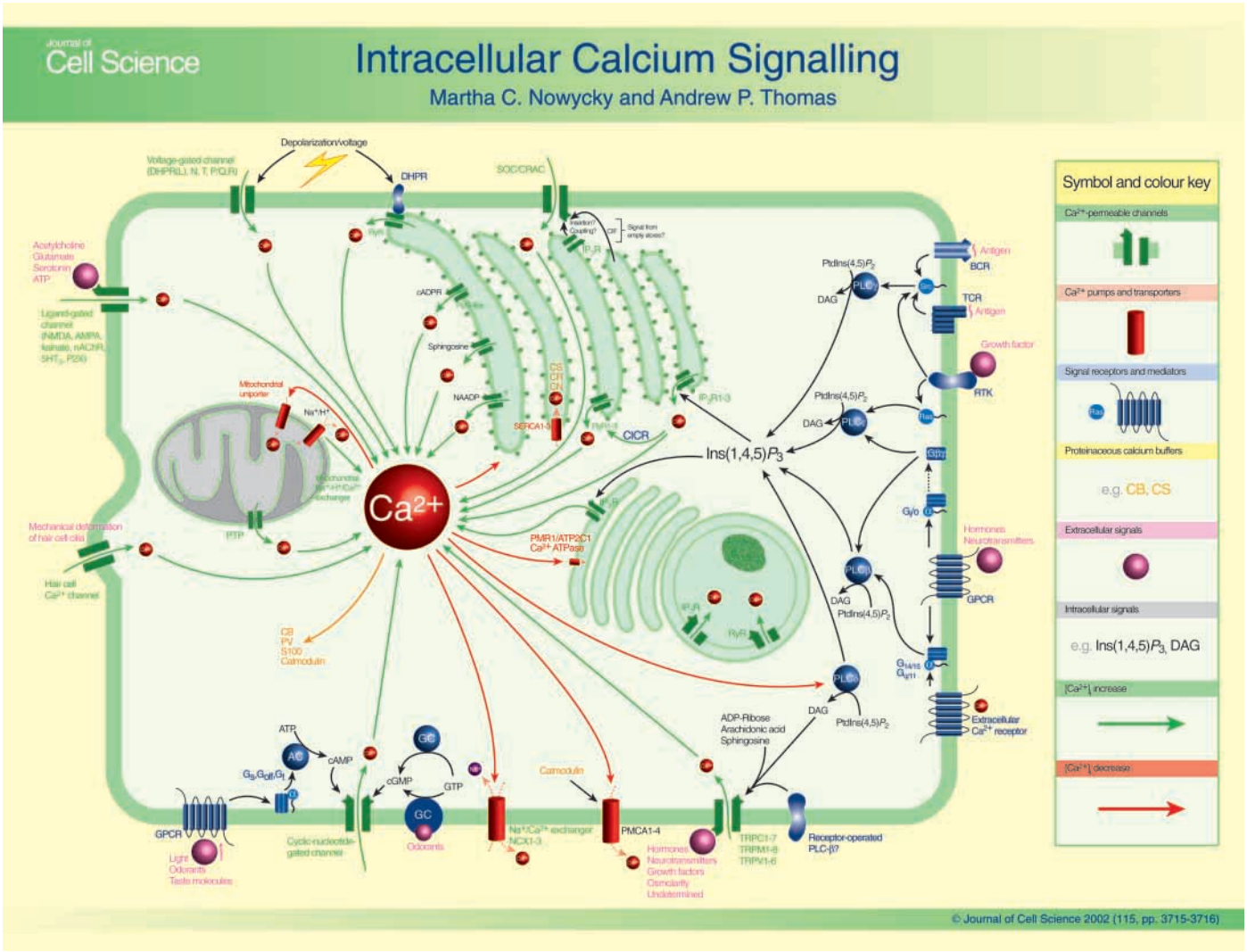
In excitable cells, the major pathway for Ca^{2+} influx is via highly Ca^{2+}-selective voltage-gated Ca^{2+} channels (VGCC). The original alphabetical nomenclature was replaced recently with standard numerical nomenclature: $Ca_V1.1$-1.4, $Ca_V2.1$-2.3, $Ca_V3.1$-3.3. In skeletal muscle cells, an additional voltage-sensitive pathway is provided by dihydropyridine receptors (DHPR, $Ca_V1.1$) that do not pass significant amounts of Ca^{2+} but are physically coupled to ryanodine receptor channels (RyR) on the sarco- and endoplasmic reticulum (ER) membrane. Indirectly, voltage also modulates the amount of Ca^{2+} entry through all voltage-independent Ca^{2+} channels by modifying the driving force for Ca^{2+} influx, with more entry at hyperpolarized potentials.

Voltage-independent Ca^{2+}-permeable channels comprise the most numerous and varied Ca^{2+}-influx pathways in cells. Many ligand-gated ionotropic channels are relatively non-selective for cations and can pass substantial amounts of Ca^{2+}. Ionotropic receptors for the transmitters glutamate (NMDA; AMPA; kainate), acetylcholine (nAChR), serotonin ($5HT_3$), and ATP (P2X) admit significant amounts of Ca^{2+}. Store-operated channels (SOC) open in response to emptying of intracellular stores. Possible mechanisms of activation include interaction with the inositol (1,4,5)-trisphosphate [Ins(1,4,5)P_3] receptor (IP_3R), a diffusible Ca^{2+}-influx factor (CIF) or channel insertion into the membrane. Ca^{2+}-release-activated Ca^{2+} channel (CRAC) is found in cells of the blood lineage and is highly Ca^{2+}-selective. Transient receptor potential channels (TRP) form a large, ancient family, that has been subdivided into three groups (TRPC, TRPV, TRPM). Most are nonspecific cation channels. TRPC channels respond indirectly to hormones and transmitters through phospholipase Cβ (PLCβ) activation and via second messengers such as



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diacylglycerol (DAG), spinghosine, ADP-ribose, arachidonic acid and other as yet unidentified signals. TRPV and TRPM families are directly or indirectly responsive to numerous sensory stimuli such as temperature and osmolarity.

Other voltage-independent channels respond to sensory stimuli. Hair cells of the ear have mechanically opened Ca^{2+}-permeant channels. Light, odorants and taste molecules operate through a signal cascade that includes activation of adenylate (AC) and guanylate cyclase (GC), and subsequent opening or closing of cyclic-nucleotide-gated channels whose gating is regulated by the cyclic nucletotides cAMP or cGMP.

With a few exceptions (ligand-gated channels, mechanosensitive channels in hair cells), voltage-independent pathways are generally activated by signaling cascades. The most common pathway involves activation of phospholipase C (PLC) and generation of Ins(1,4,5)P_3 and DAG from phosphatidylinositol (4,5)-bisphosphate [PtdIns(4,5)P_2]. Hormones and neurotransmitters can bind to >1000 G-protein coupled receptors (GPCR). The Gα subunit of the heterotrimeric Gq/11 family activates PLCβ. GPCR coupling to Gi/o can also activate PLCβ, but through the βγ subunits that are liberated in large quantities. Other members of the PLC family can be activated by growth factors that activate receptor tyrosine kinases (RTK; PLCγ), Ras (PLCε), and intracellular Ca^{2+} (PLCδ). PLCγ is also activated by antigen stimulated activation of non-receptor tyrosine kinases such as Src via binding to T-cell receptors (TCRs) and B-cell receptors (BCRs).

Ca^{2+} release from intracellular stores is mediated by ryanodine (RyR) and IP_3R channels. These two types of intracellular channel have substantial homology in their transmembrane channel-forming domains, and at least three distinct isoforms of both RyR and IP_3R have been identified. RyR are activated by a rise in intracellular Ca^{2+} – Ca^{2+}-induced Ca^{2+} release (CICR). In addition there are RyR-like channels activated by cyclic ADP-ribose (cADPR), sphingosine and a distinct Ca^{2+}-release pathway activated by nicotinic acid adenine dinucleotide phosphate (NAADP).

Within Ca^{2+}-storing organelles, Ca^{2+} ions are bound to specialized Ca^{2+}-buffering proteins. These include calsequestrins (CS), calreticulins (CR) and calnexins (CN). In the cytosol, there are mobile Ca^{2+} buffers that blunt Ca^{2+} spikes and assist in redistribution of Ca^{2+} ions. These include the calbindins (CB), paravalbumin (PV), calmodulin and S100 protein families.

In contrast to the striking variety of mechanisms for inducing extracellular Ca^{2+} influx, Ca^{2+} extrusion to the extracellular space is largely limited to two families of proteins: the plasma membrane Ca^{2+} ATPase (PMCA) and the Na^+/Ca^{2+} exchanger. Intracellular Ca^{2+} is also lowered by Ca^{2+} uptake into cellular organelles via a variety of organelle-specific pumps and transporters. Uptake into the ER is regulated by the sarco- and endoplasmic reticulum Ca^{2+} ATPase (SERCA) family. Uptake into mitochondria is mediated by the mitochondrial Ca^{2+}-uniporter. Uptake into Golgi is mediated by the P-type Ca^{2+}-transport ATPase (PMR1/ATP2C1). Mitochondria can release Ca^{2+} via the mitochondrial Na^+-H^+/Ca^{2+} exchanger and, under some circumstances, the permeability transition pore (PTP). As a result of the interplay between mitochondrial Ca^{2+} uptake and release pathways, these organelles are thought to play an important role in modulating cytosolic Ca^{2+} signals derived from other channels. Release from the Golgi and nuclear membrane takes place via intracellular channels similar to those found in the ER [IP_3R, RyR].

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