EDITORIAL

Advances in intracellular Ca^{2+} signalling

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It was over 125 years ago that Sidney Ringer, working in his laboratory at University College Hospital in London, discovered the requirement for calcium in maintaining contraction of the heart. Similar findings were subsequently made in many different physiological systems, leading Nobel Laureate Otto Loewi to exclaim in 1959: 'Ja, Kalzium! Das ist alles'. Loewi's proclamation is not unfettered hyperbole. We now know that cytoplasmic Ca^{2+} can control myriad responses within a cell, ranging from neurotransmitter release operating over a sub-milliseconds time scale to cell growth and proliferation, which can occur hours to days after termination of the initial Ca^{2+} signal (Clapham, 2007). Cytoplasmic Ca^{2+} can also trigger cell death through the highly orchestrated sequence of events that develops during apoptosis. Inherent to the use of a multifarious messenger like Ca^{2+} is the old chestnut of specificity: how are some responses within a cell activated and not others when intracellular Ca^{2+} rises? What has become apparent in recent years is that where Ca^{2+} goes up within the cytoplasm and for how long it stays up are key factors that help determine a selective response (Parekh, 2011). Moreover, dysregulation of the spatial or temporal profile of the Ca^{2+} signal can contribute to patho-physiology, occasionally with devastating consequences.

Intracellular Ca^{2+} can be rapidly increased through the opening of Ca^{2+}-permeable ion channels in either intracellular stores like the endoplasmic reticulum or in the plasma membrane. The kinetics of the Ca^{2+} signal are dictated by properties of the channels themselves, local Ca^{2+} buffering and Ca^{2+} clearance mechanisms including Ca^{2+} pumps and Na^{+}–Ca^{2+} exchange. Important advances in these areas, and how they impact on cell function in health and disease, were described in a Gordon Research Conference on intracellular Ca^{2+} signalling, held in 2015 at the Sunday River Resort in Newry, Maine, USA. This issue brings together five review articles from speakers at that meeting which reflect the versatility of Ca^{2+} signalling.

Ambudkar provides a comprehensive overview of Ca^{2+} signalling in exocrine glands and how the signals can be hijacked in diseases such as autoimmune primary Sjögren's syndrome (Ambudkar, 2016). A major route for Ca^{2+} influx in virtually all eukaryotic cells is through store-operated CRAC channels in the plasma membrane (Hoth & Penner, 1992; Parekh & Penner, 1997). These channels are activated following InsP_3-dependent release of Ca^{2+} from the endoplasmic reticulum (ER). As store Ca^{2+} content falls, the ER Ca^{2+} sensors STIM1 and STIM2 migrate towards the plasma membrane to open Orai proteins, the pore-forming subunits of the CRAC channels (Soboloff *et al.* 2012; Amcheslavsky *et al.* 2015). The author highlights a form of channel amplification in which Ca^{2+} entry through Orai1, which by itself is sufficient to activate NFAT transcription factors (Kar & Parekh, 2015), stimulates insertion of TRPC1/TRPC3 channels (Ambudkar, 2016). The presence of these large conductance non-selective cation channels leads to different intracellular Ca^{2+} signatures with distinct downstream consequences.

Bogeski and colleagues discuss the emerging role of the STIM/Orai pathway in cancer focusing on melanoma (Stanisz *et al.* 2016), the most lethal form of skin cancer. Melanoma arises from malignant transformation of melanocytes, melanin-pigment-synthesizing cells that occupy the epidermal basement layer of the skin. Melanin helps protect against UV irradiation. It turns out that Orai1, gated by STIM2 in this system, controls proliferation, migration, invasion and melanin production in melanocytes and melanoma. Targeting CRAC channels could therefore be an effective strategy for reducing the risk of UV-driven melanoma following excessive sun exposure.

To activate Orai channels, ER-resident STIM protein multimers migrate across the ER to occupy specialized regions juxtaposed against the plasma membrane. At these specialized ER–plasma membrane junctions, STIM is close enough to bind to and open Orai channels. How the junctions form, how they are maintained and how the compartmentalized Ca^{2+} signals are decoded are described by Tepikin and colleagues (Okeke *et al.* 2016). What emerges is an appreciation of how versatile these regions actually are, integrating Ca^{2+}, cAMP and redox signalling with lipid transport between the ER and plasma membrane.

Physiologically, CRAC channels are activated by store depletion following InsP_3-driven Ca^{2+} release from the ER. Prole and Taylor describe how InsP_3 receptors form signalling hubs through interactions with proteins that regulate channel activity and which can be regulated themselves (Prole & Taylor, 2016). Additional proteins located within the hubs are activated by local Ca^{2+} flux through the InsP_3 receptors. This latter process provides a means whereby spatially restricted Ca^{2+} signals on the ER surface can be selectively guided to downstream effectors. The number of proteins that are thought to interact with the InsP_3 receptor is sizeable, which perhaps helps explain why the InsP_3 receptor is so large compared with most other ion channels.

An interesting form of InsP_3 receptor regulation, described by Yule and colleagues (Wang *et al.* 2016), is through cleavage by caspases at a DEVD substrate motif site between amino acids 1888 and 1891. The receptor is cut into two fragments: a larger N-terminal component that harbours the InsP_3 binding site and a smaller C-terminal stump with the channel pore. Despite cleavage, the fragmented receptor migrates at the same molecular weight as the full length receptor, indicating the former preserves the same tetrameric arrangement as the normal protein. Remarkably, the cleaved receptor retains gating by InsP_3 in response to Gq-coupled receptor activation (Wang *et al.* 2016). How fragmentation alters the overall spatiotemporal profile of InsP_3-driven Ca^{2+} release is unclear but one could well imagine altered regulation by components within the signalling hub described by Taylor and colleagues. Ryanodine-sensitive Ca^{2+} release channels also maintain function after proteolytic cleavage (George *et al.* 2004), suggesting fragmentation might be a form of long-term modulation in Ca^{2+} release channels that helps them adapt to changes in the environment.

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We have seen significant strides in our understanding of Ca^{2+} signalling over the last couple of years in all areas of Ca^{2+} homeostasis. However, these advances have spawned new questions, which are being vigorously pursued. We can look forward with great anticipation to further breakthroughs in the coming years.

References

Ambudkar IS (2016). Calcium signalling in salivary gland physiology and dysfunction. *J Physiol* **594**, 2813–2824.

Amcheslavsky A, Wood ML, Yeromin AV, Parker I, Freites JA, Tobias DJ & Cahalan MD (2015). Molecular biophysics of Orai store-operated Ca^{2+} channels. *Biophys J* **108**, 237–246.

Clapham DE (2007). Calcium signaling. *Cell* **131**, 1047–1058.

George CH, Jundi H, Thomas NL, Scoote M, Walters N, Williams AJ & Lai FA (2004). Ryanodine receptor regulation by intramolecular interaction between cytoplasmic and transmembrane domains. *Mol Biol Cell* **15**, 2627–2638.

Hoth M & Penner R (1992). Depletion of intracellular calcium stores activates a calcium current in mast cells. *Nature* **355**, 353–356.

Kar P & Parekh AB (2015). Distinct spatial Ca^{2+} signatures selectively activate different NFAT transcription factor isoforms. *Mol Cell* **58**, 232–243.

Okeke E, Dingsdale H, Parker T, Voronina S & Tepikin AV (2016). Endoplasmic reticulum–plasma membrane junctions: structure, function and dynamics. *J Physiol* **594**, 2837–2847.

Parekh AB (2011). Decoding cytosolic Ca^{2+} oscillations. *Trends Biochem Sci* **36**, 78–87.

Parekh AB & Penner R (1997). Store-operated calcium influx. *Physiol Rev* **77**, 901–930.

Prole DL & Taylor CW (2016). Inositol 1,4,5-trisphosphate receptors and their protein partners as signalling hubs. *J Physiol* **594**, 2849–2866.

Soboloff J, Rothberg BS, Madesh M & Gill DL (2012). STIM proteins: dynamic calcium signal transducers. *Nat Rev Mol Cell Biol* **13**, 549–565.

Stanisz H, Vultur A, Herlyn M, Roesch A & Bogeski I (2016). The role of Orai/STIM calcium channels in melanocytes and melanoma. *J Physiol* **594**, 2825–2835.

Wang L, Alzayady KJ & Yule DI (2016). Proteolytic fragmentation of inositol 1,4,5-trisphosphate receptors: a novel mechanism regulating channel activity? *J Physiol* **594**, 2867–2876.