

Decoding Ca^{2+} signals through cAMP

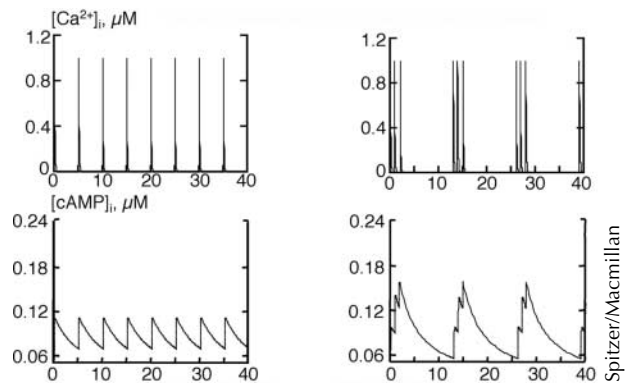
Transient changes in intracellular Ca^{2+} concentrations drive many biological processes, from gene transcription to growth cone turning. Ca^{2+} elevations can initiate cAMP oscillations, but new results suggest that only specific patterns of Ca^{2+} have this ability. Yuliya Gorbunova (University of Medicine & Dentistry of New Jersey, Piscataway, NJ) and Nicholas Spitzer (University of California, San Diego, CA) anticipate that their results may shift the focus in the field from Ca^{2+} spike frequency to spike timing and pattern.

The two examined reciprocity in Ca^{2+} /cAMP signaling in embryonic spinal neurons using fluorescent indicator dyes. In culture, increases in cAMP levels increased the frequency of Ca^{2+} spikes in neurons, whereas decreasing cAMP production had the reverse effect. Blocking Ca^{2+} spikes inhibited cAMP increases. Only specific patterns of induced Ca^{2+} transients caused cAMP transients—singlets of Ca^{2+} spikes were ineffective at producing cAMP oscillations, but triplets of Ca^{2+} spikes in rapid succession were effective. Spitzer predicts the resulting cAMP oscillations control transcriptional regulation of genes responsive to these frequencies of Ca^{2+} transients.

They then derived a mathematical model to characterize cAMP/ Ca^{2+} reciprocity. “If cells are generating this activity naturally, it’s probably important,” says Spitzer. The model will

allow them to test certain predictions quickly and determine the interest of the results to pursue in biological experiments. For instance, the model predicts that coincident elevation of both cAMP and IP3 in a cell results in negative interaction between the messengers; only specific combinations of concentrations of the two produce Ca^{2+} and cAMP transients. Testing this hypothesis in cells may help reveal how neurons coordinate multiple signals to produce the appropriate result. ■

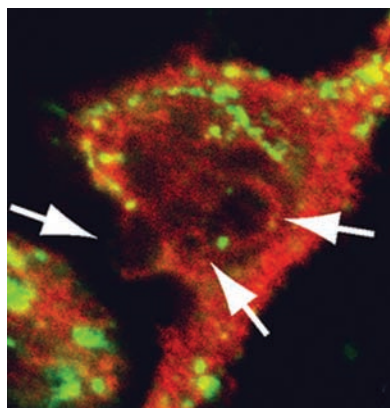
Reference: Gorbunova, Y., and N. Spitzer. 2002. *Nature*. 418:93–96.



Triple, but not single, Ca^{2+} spikes produce cAMP oscillations.

The ER contributes to engulfment

New results from Etienne Gagnon, Michel Desjardins (Université de Montréal, Montreal, Canada), and colleagues finally explain how a macrophage cell produces enough membrane to engulf material as large as itself—it uses large contributions of membrane from the ER. This is the first demonstration that the ER can fuse with the plasma membrane (PM).



ER proteins (red) are found in early phagocytic structures (arrows).

In a previous proteomics experiment, Desjardins’ group found several ER-associated proteins in phagosome preparations. But their first thought was contamination, as phagocytosis is widely considered to be a function of the PM. “This was something from the textbooks we all did not question,” Desjardins says. “It was not our aim to challenge this idea.” However, the new immunogold and immunocytochemical experiments clearly showed a distribution of ER marker proteins such as calnexin and calreticulin throughout the phagosome membrane.

Inhibition of phagocytosis revealed direct contacts between the ER and the PM at the sites of engulfment, where the two membranes apparently fused. ER contribution occurred early in the process, as the markers were also seen on the phagocytic cup, a structure formed before the phagosome fully surrounds the material to be engulfed. The ER

contributed to phagocytosis mediated by various receptors, and even when only small amounts of membrane were required, indicating that its contribution is a general phenomenon in macrophages.

Neutrophils, in contrast, did not use ER membrane for phagocytosis. Desjardins believes this may reflect the different strategies of the two cell types. The antigen-presenting function of macrophages would be enhanced by the entry of pathogens directly into the ER, where they could undergo controlled trimming and antigen presentation, by both MHC class I and II molecules, in a nonlytic environment. Because neutrophils function primarily to engulf and destroy pathogens rapidly, they may not have the need for an ER-mediated phagocytic system, and may use other membrane sources, such as azurophilic granules, instead. ■

Reference: Gagnon, E., et al. 2002. *Cell*. 110:119–131.