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Introductory Editorial

New mechanisms and functions in Ca^{2+} signalling

What progress has been achieved since the discovery in the1880's by S. Ringer of the enormous importance of Ca^{2+} (Ringer, 1883)! This discovery was subsequently followed by other breakthroughs at an ever-increasing pace. Finally, in the last two decades, and more specifically since the discovery of inositol 1,4,5-trisphosphate ($InsP_3$) as a Ca^{2+}-releasing agent (Streb et al., 1983) and the first observation of Ca^{2+} oscillations in non-excitable cells (Cuthbertson et al., 1985), the study of Ca^{2+} signalling has acquired the status of an entire field of research. Most cell biologists and physiologists are now fully aware of the important and widespread role of $InsP_3$ in mediating Ca^{2+} release from the endoplasmic reticulum (ER), of the resulting spectacular oscillations and waves of cytosolic Ca^{2+} and of the variety of functions ensued by the latter second messenger. The basic pathways of $InsP_3$ metabolism and mode of action are rather well elucidated, as well as the mechanisms leading to the complex spatio-temporal organization of the intracellular Ca^{2+} signals (Berridge et al., 2003). However, the subject of Ca^{2+} signalling is still much richer than previously thought. Our goal is of course not to cover the whole field, especially because a number of special issues devoted to particular subdomains of the calcium dynamics have recently been published (Bootman et al., 2002; Krebs et al., 2002; Falcke and Malchow, 2003; Nilius, 2003; Paschen, 2003). The aim of this special issue is therefore rather to focus on a number of new and original aspects of Ca^{2+} signalling whereby the authors all expose the state of the art in selected topics related either to the mechanism (first part), or to the physiological implications (second part) of these highly regulated Ca^{2+} changes.

Quite naturally, this issue of *Biology of the Cell* opens with a review devoted to the new data about the $InsP_3$ receptor ($InsP_3R$), the main actor in Ca^{2+} signalling. The differential localizations of the various isoforms of the receptor, as well as the possible mechanisms of their redistribution are discussed. From this review clearly emerges the idea that $InsP_3Rs$ are dynamically regulated to adapt to the physiological status of the cell.

$InsP_3$ however is not unique as mediator of intracellular Ca^{2+} signals, and one of the reasons why the Ca^{2+} field is expanding so much is that more and more players appear to take part in Ca^{2+} regulation. This idea is clearly apparent in the second review in which the authors discuss Ca^{2+} mobilization by mechanisms that do not rely on $InsP_3$ and especially focus on the most-recently discovered Ca^{2+}-releasing messenger, NAADP, for which the mode of action is still poorly understood.

For all signal transduction pathways, cell-to-cell variations are well known to occur, and Ca^{2+} signalling does certainly not escape this rule. A striking case in which Ca^{2+} signalling seems to be specifically adapted to the cell's need is that of eggs before, during and after fertilization. The main ingredients are always the same ($InsP_3$, Ca^{2+} release from the ER, regulation by Ca^{2+} of the activity of the diverse receptor isoforms, etc.) while the details of the regulation are specific. But when the details pertain to the onset of life, they acquire a fascinating character. Diverse aspects of Ca^{2+} signalling at fertilization are treated here in 2 reviews. One of them is devoted to the ascidian egg, a prototypic species that, similarly to mammals, displays Ca^{2+} oscillations. The second contribution in the field presents the state of the art concerning the 'mysterious' sperm factor responsible for $InsP_3$ generation at fertilization.

Finally, in most cell types, it is clear that $InsP_3$-induced Ca^{2+} release is inseparable from the process of stimulated Ca^{2+} entry, occurring after Ca^{2+}-store depletion. This mechanism, often originally called "capacitative calcium entry", but now mostly named "store-operated calcium entry" is not yet elucidated. The last review in this first part of the issue will therefore summarize the actual knowledge about this complex problem.

In the second part of the issue, some interesting physiological implications of this highly regulated Ca^{2+} signalling machinery are exposed. The first chapter is therefore related to the Ca^{2+}-regulated mechanisms of cell growth and proliferation. The two main targets are the well-known Ca^{2+}-dependent transcription factors CREB and NFAT. The activation of these nuclear processes is shown to depend on the amplitude and the spatial extent of the Ca^{2+} increase. The authors also make the point on how the manipulation of the Ca^{2+} dynamics could be used as an anti-cancer therapeutic target.

Another field full of potential therapeutic applications is of course that of immunology. The authors of the following chapter, first go through the various rather unusual characteristics of Ca^{2+} signalling in T lymphocytes: PLC activation implies here a tyrosine-kinase pathway, Ca^{2+} increases are slow and of moderate amplitude, and the role of Ca^{2+} influx (through a still unknown mechanism) is predominant. In this very thought-provocating review, the generally accepted

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concept of the formation of T-cell receptors clusters is even questioned.

Going from the immune system to the central nervous one, we enter into the world of intercellular communication between various cell types, mainly neurons, glial and microvascular cells. This state of the art review about these various and intricate pathways clearly shows that a more global view of the neural tissue needs to be developed.

Finally, the last review reveals a much less known implication of Ca^{2+} signalling, related to bacterial infection. Although in most cases the precise mechanisms involving the Ca^{2+} ions are still unknown, this review clearly shows that Ca^{2+} is a central element both to induce or to amplify the epithelial cells response to pathogenic microorganisms, as well as to allow the survival of these microorganisms.

In conclusion, it is our aim that the choice of the various topics included in this special issue of *Biology of the Cell* reflect current interests in the field of Ca^{2+} signalling and demonstrates the need for continuous research in a number of exciting areas.

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