Cellular signalling

A second messenger function for inositol tetrakisphosphate

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An entirely novel concept entered our knowledge of how receptors send signals through membranes to the cell interior when it was realized that the receptor-activated hydrolysis of phosphatidylinositol 4,5-bisphosphate yields two second messengers rather than one. Inositol 1,4,5-trisphosphate ($Ins(1,4,5)P_3$) and 1,2-diacylglycerol have different molecular targets within the cell, but they often act synergistically during the evocation of cell responses (reviewed in refs 1–3). Enzymic removal of the 5-phosphate of $Ins(1,4,5)P_3$, discovered in 1982, provided a perfectly respectable mechanism for its inactivation. In the past year or so, however, it has become increasingly clear that there is a quantitatively important alternative pathway for the rapid metabolism of $Ins(1,4,5)P_3$ in stimulated cells, as a result of which it is phosphorylated to inositol 1,3,4,5-tetrakisphosphate ($Ins(1,3,4,5)P_4$), which is then dephosphorylated to inositol 1,3,4-trisphosphate, $Ins(1,3,4)P_3$ (see my recent News and Views article[4] and refs 5,6). It has been widely expected that $Ins(1,3,4,5)P_4$ or $Ins(1,3,4)P_3$, or maybe both, would function as additional intracellular messenger(s) generated by this increasingly complex signalling system, Irvine and Moor[5] now present the first evidence in support of this hope. Using sea urchin eggs, they obtain evidence that strongly suggests that $Ins(1,3,4,5)P_4$ regulates the entry of calcium ions into these cells from the external medium.

Whittaker and Irvine[7] were the first to show that injection of $Ins(1,4,5)P_3$ into sea urchin eggs suspended in a Ca^{2+}-containing medium causes the raising of a fertilization membrane, a response which seems identical to that produced by normal fertilization by sperm. It is generally agreed that this response is mediated by a rise in intracellular Ca^{2+} that is fed both from internal Ca^{2+} stores and from the external medium. $Ins(1,3,4,5)P_4$ does not mobilize Ca^{2+} from intracellular stores[6], so it was no surprise when it failed to activate eggs[5]. But it has been clearly demonstrated that $Ins(2,4,5)P_3$ mobilizes Ca^{2+} from the same intracellular store as $Ins(1,4,5)P_3$, so its failure to raise a fertilization membrane was unexpected[5]. Irvine and Moor surmise that the key to the difference between $Ins(1,4,5)P_3$ and $Ins(2,4,5)P_3$ might lie in the ability of the former to be converted to $Ins(1,3,4,5)P_4$ in the eggs into which it is injected, and wondered whether activation requires the simultaneous presence within the eggs of $Ins(1,4,5)P_3$ and of $Ins(1,3,4,5)P_4$ derived from it. ($Ins(2,4,5)P_3$ is not an effective alternative substrate for $Ins(1,4,5)P_3$ 3-kinase, so it could not provide $Ins(2,3,4,5)P_4$ as an $Ins(1,3,4,5)P_4$ analogue.) To test this idea, eggs were incubated in a Ca^{2+}-containing medium and injected with a mixture of $Ins(1,3,4,5)P_4$ and $Ins(2,4,5)P_3$. The results are startling. This mixture of two ineffective inositol phosphates activates the eggs as effectively as $Ins(1,4,5)P_3$ alone. As with other modes of egg activation, success with the $Ins(1,3,4,5)P_4/Ins(2,4,5)P_3$ mixture requires the presence of extracellular Ca^{2+}. Irvine and Moor conclude[5] that $Ins(1,3,4,5)P_4$ is likely to be the intracellular messenger responsible for initiating Ca^{2+} entry from the exterior, and that this is somehow dependent on the prior or simultaneous $Ins(1,4,5)P_3$-triggered discharge of the intracellular Ca^{2+} store. They envisage that these two processes are coupled in some mandatory way such as that envisaged by Putney[8]: his idea is that Ca^{2+} entering from the exterior does not move directly into the cytosol, but is routed through the $Ins(1,4,5)P_3$-sensitive pool, with influx particularly rapid when this pool is either partially or fully discharged.

If future data confirm this view of events in sea urchin eggs and extend it to other cells, we now have all the key elements necessary to understand receptor-regulated Ca^{2+} mobilization into the cytosol of most stimulated cells. Of course, $Ins(1,4,5)P_3$ and $Ins(1,3,4,5)P_4$ need to be both produced and inactivated in a coordinated way. A remarkably tidy facet of this entire system is that the inositol polyphosphate 5-phosphatase that was originally detected as an $Ins(1,4,5)P_3$ 5-phosphatase may simultaneously inactivate both of these signals. □

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Atomic motion

Quantum fluctuations in sub-micron wires

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Physicists have long held the notion that measurements on a macroscopic sample are the same as the average over an ensemble of similarly prepared samples. In the past two or three years, this notion has been challenged by a combination of two factors: the ability to prepare small samples using micro-fabrication techniques; and the general availability of low temperature in the tens of millikelvin range. The typical sample dimension is 0.05 μm diameter and 1 μm long, so that these 'small' samples still contain 10^8–10^9 atoms. The surprise is that these samples, which are macroscopic on the atomic scale, already exhibit large fluctuations in their electric conductivity which also vary from sample to sample. Furthermore, theoretical developments have led to a quantitative description of this phenomenon, and point to the possibility of detecting the change in the conductivity of a small metallic sample if the sample is perturbed in the slightest manner, even in the limit of displacing a single atom.

These developments were initiated by the discovery that the resistances of small metallic wires ($0.04 \times 0.04 \times 0.7$ μm^3) exhibit random structure when a magnetic field is applied perpendicular to the wires[1]. The structure is observable below 1 K; it increases in magnitude down to 10 mK where it is about a 0.1 per cent effect, it is reproducible upon cycling of temperature and magnetic fields, and it is a signature of a particular sample.

At these low temperatures, the resistance is entirely due to the presence of impurities and imperfection in the sample and the motion of the electron through the sample must be described in terms of quantum mechanics. A particularly illuminating way of describing the low temperature conductance G (inverse of resistance) of a disordered sample was provided by Landauer[2], who showed that G is proportional to the transmission probability of the electron wave through the disordered medium. The proportionality constant is e^2/h which is a combination of fundamental constants with the dimension of conductance and equals $4 \times 10^{-5}\ \Omega^{-1}$. (The same combination is the unit of the Hall conductance in the quantized Hall effect.)