Regulation of cell growth and cell death by MAP kinase signalling pathways

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The role of InsP₃ signalling cascade in the generation of cardiac arrhythmia

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Signalling networks regulate apoptosis during inner ear development

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Programmed cell death is a critical process for normal development and tissue homeostasis. While the basic programme of execution of apoptosis is conserved, distinct regulatory signals have been described depending on the cell type and developmental stage. Particularly interesting are the opposite actions displayed by nerve growth factor (NGF), which acts either as a survival factor or as a death-inducing factor. A coherent understanding of the regulation of programmed cell death during development requires a co-ordinated study of some of the multiple signals acting on the cells. We are interested in the molecular mechanisms by which these signals initiate and pattern the vertebrate inner ear. IGF-1 is a member of a family of structurally related genes that have pleiotropic actions on development and tissue homeostasis. While the basic regulatory signals have been described depending on the cell type and context, we have explored the interactions between the pathways activated by IGF-1 to prevent apoptosis and those activated by NGF to induce cell death. We propose that the dynamic balance between levels of ceramide metabolites and the consequent regulation of Akt phosphorylation are important factors that determine whether a cell survives or dies.

Jones DR et al. (2002). Proc Natl Acad Sci USA

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Regarding the nucleus, the dampening of nuclear calcium oscillations relative to those recorded in the core cytosol can be explained by either a permeability barrier at the nuclear envelope or, alternatively, by an increased buffer capacity of the nucleus (P. Chamero, C. Villalobos, M.T. Alonso & J. García-Sancho, submitted). At present, we do not have evidence to favour either of the two alternatives. However, whatever the mechanism, the functional consequence is that transmission of the cytosolic calcium signal to the nucleus depends on the signal’s nature. Specifically, sustained calcium increases in the cytosol are faithfully transmitted into the nucleus whereas transient, oscillatory signals are strongly dampened when sensed by the nucleus. This may be a mechanism by which calcium may regulate differentially nuclear functions such as cell division or gene expression (P. Chamero, C. Villalobos, M.T. Alonso & J. García-Sancho, submitted).


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Voltage control of P2Y receptor-evoked Ca\textsuperscript{2+} release in the rat megakaryocyte: sensitivity limits and activation by action potentials

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The ability of membrane potential to modulate IP\textsubscript{3}-dependent Ca\textsuperscript{2+} release independently of Ca\textsuperscript{2+} influx has been described in a number of excitable cell types but has been most extensively studied in the non-excitatory rat megakaryocyte (MK) (Mahaut-Smith et al. 1999). We have now examined the limits of sensitivity of this phenomenon to step depolarisations and activation by action potential waveforms (APW) in the MK.

Male Wistar rats were humanely killed by CO\textsubscript{2} inhalation and cervical dislocation. Whole-cell patch clamp and [Ca\textsuperscript{2+}]\textsubscript{i} recordings from marrow MKs were conducted as described previously (Mahaut-Smith et al. 1999). Depolarising steps of increasing magnitude or duration were applied during activation of P2Y receptors (1 \mu M ADP). The peak [Ca\textsuperscript{2+}]\textsubscript{i} response showed marked heterogeneity between cells: range 23–560 nM (n = 17) for a 55 mV, 5 s step from −75 mV. A positive correlation was observed between the average [Ca\textsuperscript{2+}]\textsubscript{i} increase and amplitude of the voltage step (range 3 to 55 mV) from −75 mV. The responses for 55, 20 and 10 mV steps were 151 ± 34, 84 ± 13 and 45 ± 6 nM, respectively (mean ± S.E.M. n = 17 or 18). The most sensitive cells lacked a threshold potential and showed [Ca\textsuperscript{2+}]\textsubscript{i} increases with depolarisations of only 3 mV (n = 5). We also examined the dependence of the depolarisation-evoked [Ca\textsuperscript{2+}]\textsubscript{i} increase upon pulse duration using a step from −85 to +50 mV. The [Ca\textsuperscript{2+}]\textsubscript{i} response increased with pulse duration up to 700 ms; the average was 48 ± 15 nM (n = 9) for 250 ms compared to 25 ± 4 nM, n = 17 for 100 ms. Again, the most sensitive cells responded with a [Ca\textsuperscript{2+}]\textsubscript{i} increase to the shortest (25 ms) pulse.

These data suggest that depolarisations of only a few millivolts or tens of milliseconds are sufficient to induce a [Ca\textsuperscript{2+}]\textsubscript{i} increase, but the ventricular waveform generated a larger peak response (182 ± 12 nM, n = 6 vs. 47 ± 6 nM, n = 10).

Our data indicate that voltage control of Ca\textsuperscript{2+} release via a G-protein-coupled receptor is sufficiently sensitive to detect small voltage changes and APW. The role of this novel signalling mechanism in excitable and non-excitable tissues should therefore be considered.


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All procedures accord with current UK legislation.


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