The long and short of cell signaling

August 5 2010

Like dots and dashes from a Morse code transmission, brief and sustained cell signals can have different meanings for cell fate.

Like a telegraph transmission, the significance of a cellular signal can change greatly depending on whether it arrives as a brief 'dot' or a sustained 'dash'. For example, transient activation of extracellular receptor kinase 1/2 (ERK) by epidermal growth factor (EGF) causes cells to divide, while prolonged ERK activation induced by heregulin (HRG) instructs these same cells to differentiate.

Cell biologists have struggled to untangle the relationship between this signaling network and cell fate, but a collaborative effort between Mariko Okada-Hatakeyama at the RIKEN Center for Allergy and Immunology in Yokohama and Boris Kholodenko at University College Dublin in Ireland has achieved an important breakthrough by pairing quantitative experiments with computational modeling.

Okada-Hatakeyama's team previously examined the expression of c-fos, a so-called 'immediate early gene' whose expression is induced shortly following ERK activation, and obtained somewhat contradictory findings. "Early gene expression time-course profiles were the same regardless of whether the upstream ERK signal is transient or sustained," she says. "However, levels of Fos protein were 'all or none' for sustained and transient signals, respectively."

Based on an initial interpretation of their computational model of this pathway, Okada-Hatakeyama, Kholodenko and colleagues proposed that the effects of both HRG and EGF on c-fos expression were modulated purely by dual-specificity phosphatases (DUSPs), enzymes that inhibit ERK's capability to induce c-fos. However, experiments with a forced reduction of DUSP in cultured cells did not fully replicate these predictions. "There were long and serious discussions whether [our experiment] was working properly or the model was wrong," says Okada-Hatakeyama.

This reassessment led to experiments that enabled the researchers to demonstrate the existence of a second, previously unknown mechanism for repression of c-fos expression that is triggered only in response to HRG. Together, these two ERK-activated 'negative feedback' systems appropriately control c-fos transcription in the process of cellular differentiation.

In parallel, their model also revealed how the combination of ERK-induced c-fos expression and sustained signaling activity by ERK outside the nucleus lead to steady production of c-Fos protein. This system architecture results in a highly stable signaling arrangement that filters out extraneous background noise and induces all-or-none output, according to Okada-Hatakeyama. "We learned from this study that cells possess very simple but robust system structures that can fight against unwanted perturbations," she says. "This cellular signaling network is

still a ‘black box’ and what we can do [with computational modeling] is very much limited … but we hope to [untangle] the cell decision program someday.”

More information:

-- Nakakuki, T., Birtwistle, M.R., Saeki, Y., Yumoto, N., Ide, K., Nagashima, T., Brusch, L., Ogunnaike, B.A., Okada-Hatakeyama, M. & Kholodenko, B.N. Ligand-specific c-Fos expression emerges from the spatiotemporal control of ErbB network dynamics. Cell 141, 884-896 (2010). www.cell.com/abstract/S0092-8674(10)00373-9
-- Nagashima, T., Shimodaira, H., Ide, K., Nakakuki, T., Tani, Y., Takahashi, K., Yumoto, N., & Hatakeyama, M. Quantitative transcriptional control of ErbB receptor signaling undergoes graded to biphasic response for cell differentiation. The Journal of Biological Chemistry 282, 4045-4056 (2007). www.jbc.org/content/282/6/4045.abstract

Provided by RIKEN