Eggs never forget

A simple positive feedback loop is a memory aid for egg cells that pushes their metabolism in one direction, based on research from Wen Xiong and James Ferrell (Stanford University, Stanford, CA). According to Ferrell, the work puts “some biochemical meat on the bones of commitment.”

That commitment occurs during egg cell maturation. Frog egg cells mature from a paused G2-like state in response to a hormone stimulus. Even a transient stimulus pushes cells through maturation to meiosis II via a kinase/phosphatase cascade of ~15 proteins, including p42 MAPK, cyclin B/Cdc2, and Cdc25. As phosphorylation is reversible but maturation is not, cells must somehow remember their hormone encounter. The authors now show that this memory lies in a positive feedback loop in the p42 pathway.

Feedback is provided by the protein Mos, which activates p42, which in turn promotes Mos accumulation. By blocking the effects of Mos, the authors show that p42 MAPK activation becomes reversible in the absence of positive feedback. The simplicity of positive feedback loops explains why researchers stumble upon them so often, according to Ferrell, who hopes “clever systems biologists will uncover other examples of irreversible cell fates established by positive feedback loops.”

Reference: Xiong, W., and J.E. Ferrell. 2003. Nature. 426:460–465.

Calcium makes a fast getaway

Dendrites are like a busy phone exchange. A single neuron can have thousands of synapses talking to its dendrites. Some dendrites are able to separate the input from neighboring synapses with spines that act as morphological barriers of synaptic input by restricting calcium diffusion. Many neurons lack spines, however, thus causing speculation that these dendrites might lack synaptic specificity. But Jesse Goldberg, Rafael Yuste (Columbia University, New York, NY), and colleagues now show that these aspiny dendrites are able to compartmentalize—by restricting calcium domains in space and time.

The group imaged calcium dynamics in aspiny dendrites, where synaptic activation created a fast, short-lived, and highly localized calcium influx. However, they saw no morphological structures that could contain the signal. Rather, says Goldberg, “the key to localization is fast kinetics.” This is provided by calcium-permeable glutamate receptors of the AMPA family (CP-AMPAs), which turn on and off rapidly. The strong influx of calcium was also quickly purged by the Na\(^+/Ca^{2+}\) exchanger. These effects combined to limit calcium diffusion to a space on the order of the size of a synapse.

As expected based on these results, aspiny dendrites tend to have CP-AMPAs rather than the slower NMDA class of glutamate receptors. Goldberg believes the results also show that “any source of calcium can be highly localized without morphological boundaries” as long as the kinetics are right.

Reference: Goldberg, J.H., et al. 2003. Neuron. 40:807–821.

Knocked down a Notch with age

As we age, it seems to be increasingly difficult to recover from injuries. According to research from Irina Conboy, Thomas Rando, and colleagues (Stanford University and the Palo Alto VA Medical Center, Palo Alto, CA), part of the blame for this age-related decline belongs to lazy stem cells that sit idly by rather than repair injuries.

Normally, injuries to muscle tissue activate the stem cell-like satellite cells, which then multiply and differentiate into myoblasts that can fuse with and thus repair injured muscle fibers. The injury-induced proliferation is a function of the Notch pathway. But Rando’s group shows that satellite cells in older animals are unable to activate Notch and so do not repair injured muscle.

Notch gets inactivated because aged muscle cells do not up-regulate Delta, the extracellular Notch ligand. In young or adult mice, Delta expression was induced by injury, and satellite cells promoted tissue repair. Repair could be prevented by blocking Notch activation. Wound repair was restored in aged mice by antibody activation of Notch. In the future, a blood-borne nonimmunogenic Delta mimic might enhance muscle regeneration in the elderly.

It is unclear why or how Delta induction fails in older animals. Declining healing powers may be an evolutionary advantage, as some biologists argue that aging, by getting rid of post-reproductive individuals, is beneficial to the population as a whole.

Reference: Conboy, I.M., et al. 2003. Science. 302:1575–1577.