**Research Roundup**

**Keeping RNA away from DNA**

Newly transcribed RNA represents a threat to genomic stability, say Xialu Li and James Manley (Columbia University, New York, NY). They find that, in metazoan cells, the threat is neutralized by a splicing factor that coats RNA as it emerges from RNA polymerase.

The danger arises because nascent RNA can anneal to the template DNA strand, thus forming an R loop. The non-transcribed strand is left as a single strand, potentially susceptible to attack by nucleases.

Bacteria combat this tendency by tightly coupling translation to transcription. In eukaryotes, this is not an option as transcription and translation are nuclear and cytoplasmic, respectively.

Without an ASF coat, transcribed RNA interferes, resulting in DNA fragmentation.

Li and Manley did not set out to discover a genome-protective mechanism, but chanced upon it while studying ASF/SF2. The Columbia team put this splicing protein under the control of a tetracycline-responsive promoter. Shutting it off led to cell death, but many revertants became resistant to tetracycline repression.

The ASF transgene in the revertants had, along with many other genes, been shuffled into new areas via DNA rearrangements. Sure enough, markers of DNA double strand breaks appeared within 12 h of turning off ASF, and fragmented DNA appeared within 24 h. These changes were not seen with the tetracycline-mediated shut-off of other essential genes.

R loop structures appeared during the shut-off, and all these shut-off symptoms could be abolished by overexpression of RNase H, which can degrade the RNA in RNA–DNA hybrids. In vitro, ASF suppressed R loop formation during transcription as long as the transcribing RNA polymerase II was phosphorylated on its COOH-terminal domain, as it is in vivo. This phosphorylated domain was already shown to recruit ASF to the transcription reaction.

R loops are not always a bad thing. In B cells they are essential for initiating the DNA rearrangements that mediate class switching of antibody heavy chains. Keeping this machinery away from nascent RNA in other cell types may be one important, presplicing function of ASF and related proteins.

Reference: Li, X., and J.L. Manley. 2005. *Cell*. 122:365–378.

**An optical brain**

Green algae use a light-activated ion channel to control phototaxis. Now, Edward Boyden, Feng Zhang, Karl Deisseroth (Stanford University, Stanford, CA), and colleagues have used the same channel to control the rapid spiking activity of neurons.

Experimental control of neural activity has become more and more sophisticated, with glutamate uncaging and multineuron patch clamping allowing the targeting of a specific neural area. But there is a catch. “You can’t target cell types in that way,” says Deisseroth. Usually the individual cell types “are sparsely embedded in the networks.”

The obvious solution to this is genetics. Promoters to drive expression in specific cell types are available, as many of the interneuron types express unique neuropeptides or other markers. Initial attempts have met with partial success, but the complexity of the introduced signal cascades has meant that control has been on the order of seconds and minutes rather than milliseconds.

The Stanford group used rapid optical switches plus the single component channelrhodopsin-2 from the green alga *Chlamydomonas reinhardtii*. After lentivirus infection of rat neurons with their gene construct, blue light resulted in rapid depolarizing currents. Repeated light pulses could elicit spike trains typical of active neurons, with patterns that were reproducible in either the same or different neurons. In the absence of light, the resting potential, response to injected current, and cell health were unaffected.

Deisseroth is interested in how certain cell types connect with others, and what specific function each one provides. He plans to apply the new technique in the mouse or rat hippocampus to get at some of the more enigmatic functions—such as mood—controlled by this brain region. Experiments with brain sections may be followed by experiments in live animals using optical fibers and 2-photon excitation.

Reference: Boyden, E.S., et al. 2005. Nat. Neurosci. doi:10.1038/nn1525.