Research Roundup

RNA de-inhibition

Small RNAs are famous for their gene-silencing ability. But new results from Tomoko Kuwabara, Fred H. Gage (Salk Institute, La Jolla, CA), and colleagues show that some tiny RNA species turn genes on, not off.

This new class of RNAs is needed to make neurons. “Small double-stranded RNAs exist in reasonably high concentrations in cells that have just committed to neuronal lineages,” says Gage. These RNAs are homologous to a promoter sequence called NRSE/RE-1, which is found in a wide range of genes that are expressed only in neurons. In other cell types, these genes are known to be shut off by the NRSE/REST repressor.

The group shows that this repressor becomes an activator when NRSE dsRNAs are around. As a result, neuronal genes are turned on, and multipotent adult neural stem cells become neurons.

The NRSE/REST protein binds strongly to the dsRNA, and the two probably sit on promoters as a complex. When both are present, histone acetylases and chromatin-remodeling proteins replace the deacetylases and methyl-DNA binding proteins that are found at neuronal gene promoters when only NRSE is expressed.

The dsRNAs are found in regions of the hippocampus where neurons are differentiating, and their destruction prevents cultured cells from becoming neurons in response to inducing signals. A single molecule RNA switch that creates an entire lineage may not, however, be found outside neurons. “It’s an unusual case,” says Gage, “because of NRSE. It binds to so many promoters that it makes the RNAs generalizable.”

Reference: Kuwabara, T., et al. 2004. Cell. 116:779–793.

Cholesterol hastens Alzheimer’s

Results from Qinghai Zhang, Jeffery Kelly (Scripps Research Institute, La Jolla, CA), and colleagues suggest that evil metabolites may accelerate Alzheimer’s disease (AD) by promoting protein misfolding. This folding effect may explain why inflammation and high cholesterol are risk factors for AD.

AD results from aggregates of a misfolded form of amyloid β peptide (Aβ). Misfolding occasionally results from processing flaws or mutations in the Aβ precursor, but most patients have normal Aβ. Zhang et al. show that even normal Aβ folds abnormally when cholesterol by-products modify it.

Cholesterol itself did not affect Aβ, but cholesterol modified by reactive oxygen species (which are produced during inflammation) to generate an aldehyde group reacted with Aβ and made it more hydrophobic. This altered form aggregates at much lower concentrations than does normal Aβ--concentrations that are found in the brain.

Although brain samples did not show higher levels of the cholesterol aldehydes in AD patients, only small amounts of these metabolites are needed to jump start aggregation. “The creation of compounds that are reactive could be from an event occurring years before an individual presents with AD,” says Kelly. So, as boxers already know, one good knock on the head might do more lasting damage than just a fleeting headache.

Reference: Zhang, Q., et al. 2004. Proc. Natl. Acad. Sci. USA. 10.1073/pnas.0400924101.

The two faces of Mad2

Sequence dictates structure, but for Mad2, one structure is not enough. New results from groups led by Hongtao Yu and Josep Rizo (University of Texas Southwestern, Dallas, TX) show that Mad2 adopts two distinct conformations and that checkpoint activation may consist of switching Mad2 to the right form.

Mad2 holds up anaphase until every chromosome is properly attached to the spindle. Past structural studies of Mad2 showed that Mad1 (its activator), and Cdc20 (its anaphase-halting target) share the same binding site. “It would seem,” says Rizo, “that [Mad1] would be a competitor rather than an activator because they bind in the same place.” But the newly identified second conformation suggests an answer to this puzzle—Mad1 may put Mad2 in an active conformation that is maintained even when the Mads separate.

The two forms can be distinguished based on column chromatography and NMR. The active form has a higher affinity for Cdc20 than does the other form and blocks anaphase in oocyte extracts. In vivo, sequestration of only the active form thwarts the checkpoint.

The forms interchange in vitro very slowly. A fragment of Mad1, however, accelerates transformation of the inactive into the active form. Some Mad2 is always complexed with Mad1 in cells, so the question now is what tells Mad1 to toss off Mad2 (in its active form) so it can bind to Cdc20.

Reference: Luo, X., et al. 2004. Nat. Struct. Mol. Biol. 10.1038/nsmb748.