Nucleotides: saviors of the cell

Nucleotides are the building blocks of DNA and the cell’s energy currency. Now, a report by Dhyan Chandra, Dean Tang (University of Texas, Smithville, TX), and colleagues reveals that these multifunctional molecules are also bodyguards, protecting healthy cells from apoptosis.

The apoptotic cascade unfolds when failing mitochondria leak cytochrome c (cyt c), which then binds to and oligomerizes the caspase activator called Apaf1. Previous experiments showed that low concentrations of nucleotides, in the form of ATP or dATP, were needed for cyt c to bind to Apaf1.

The new results show that higher concentrations of ATP prevent apoptosis. At these higher levels, which match those found in healthy cells, the nucleotides bound up cyt c, thus preventing it from attaching to its Apaf1 partner.

The inhibition was overcome by artificially increasing cyt c levels or decreasing nucleotide concentrations. In healthy cells, sufficient nucleotide levels probably prevent small mitochondrial leaks from triggering death by sequestering the cyt c. Only with persistent cell death signals or unusually low nucleotide levels would cyt c overcome the nucleotide brake.

Low nucleotide levels, the group also shows, are induced by apoptotic signals and anticancer drugs such as etoposide. ATP production probably drops as a result of mitochondrial injury, but what causes the levels of the other nucleotides to drop is unclear as yet. JCB

Reference: Chandra, D., et al. 2006. Cell. 125:1333–1346.

Positioning proteasomes

Activity produces waste, so it makes sense to position waste disposal facilities close to sites of activity. Baris Bingol and Erin Schuman (California Institute of Technology, Pasadena, CA) have discovered that neurons do just that, recruiting proteasomes to active dendritic spines.

Dendritic spines must construct and destroy many proteins as they respond to synaptic excitation. Protein synthesis machinery has been shown to sit locally in spines to make protein when needed. Indication that the degradation machinery [proteasomes] might also serve its function locally came from Bingol’s discovery that adjacent synapses in the same neuron contained different amounts of proteasome.

Investigating the dynamics of this varied distribution, the team observed that excitation of neurons drove proteasomes from the shafts to the spines within minutes. Proteasome levels then remained high in the spines for up to an hour. Ubiquitinated proteins, targeted for destruction, also initially increased, but shortly thereafter decreased as the proteasomes arrived and got to work. Thus, the study shows that proteasomes are dynamic machines that are capable of moving toward their targets.

The increase in spine proteasome levels was due partly to recruitment and mostly to sequestration, and excitation led to an increased association of proteasomes with the actin cytoskeleton, suggesting a possible mechanism for activity-dependent localization. Investigating the molecular mechanics of actin binding would be the sensible next step, says Bingol. JCB

Reference: Bingol, B., and M.E. Schuman. 2006. Nature. doi:10.1038/nature04769.

The fragility factor

Prion proteins with the same amino acid sequence but different biophysical and biochemical structures show different pathological severities. A study of a yeast prion model, by Motomasa Tanaka, Jonathan Weissman, and colleagues (University of California, San Francisco, CA) reveals that a prion’s power is determined by aggregate stability—or, rather, lack of it.

Prions replicate by recruiting their normally folded counterparts into large aggregate fibers, which then break up to form new prion particles, capable of recruiting and converting further normal forms. A shortened version of the yeast protein Sup35, called SupNM, can misfold into various prion forms. These forms seed aggregates that result in phenotypes of reproducibly different strengths.

To investigate the basis for this difference, Weissman’s team looked at how fast the SupNM-derived aggregate fibers elongated. Contrary to expectations, they found that the most potent form, Sc4, had the slowest growth. However, this slow growth was accompanied by increased amyloid fragility—the fibers fell apart more often.

The potency of the Sc4 form was thus explained not by aggregate size or growth rate but instead by its propensity to break into new infectious prion particles. If the same physical basis of infectivity holds true for mammalian prions, then designing therapies that stabilize prion aggregates might slow or even stop disease progression.

It would be of interest to determine whether the specific structure of the Sc4 form could explain its increased aggregate fragility. Indeed, such experiments are “high on our list,” says Weissman. JCB

Reference: Tanaka, M., et al. 2006. Nature. doi:10.1038/nature04922.