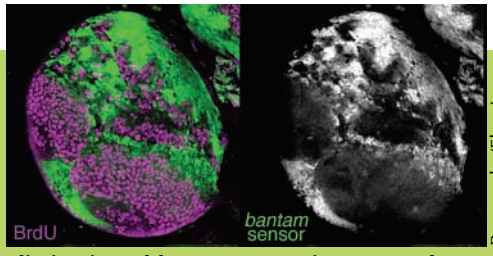
Research Roundup

MicroRNAs make big splash in apoptosis



Brennecke/Elsevier

Elimination of *bantam* expression (green) by an miRNA allows proliferation as illustrated by BrdU incorporation (purple).

Hundreds of microRNAs are encoded in animal genomes, yet the function of only two were known until recently. That number has now doubled with the identification of two miRNAs, *mir14* and *bantam*, both of which appear to regulate cell death in *Drosophila*, according to reports from Peizhang Xu, Bruce Hay (California Institute of Technology, Pasadena, CA), and colleagues and from Julius Brennecke, David Hipfner, Alex Stark, Rob Russell, and Stephen Cohen (EMBL, Heidelberg, Germany).

Cohen's group went looking for genes involved in growth control using a P-element–based overexpression screen. They found *bantam*, an miRNA, that when overexpressed causes a suppression of cell death and an increase in cell proliferation.

Using a computer program designed to identify miRNA targets, they found that bantam controls apoptosis by binding to *hid* mRNA, suppressing its translation and blocking its pro-death activity. They have not yet found the target mRNA involved in the proliferation portion of the bantam phenotype, but they have ruled out a number of the "usual suspects," says Cohen. Identification of miRNA target genes has been a stumbling block thus far in the miRNA field. The group is currently working to further validate their computational method.

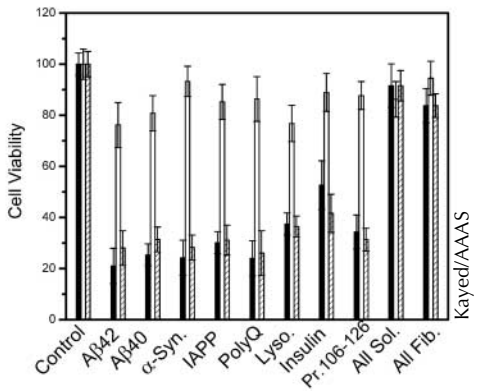
Xu et al., on the other hand, found *mir14* and several other miRNAs in a large-scale genetic screen designed to identify suppressors of apoptosis. Out of 7,000 chromosomes screened over four years ago, they had ten hits, six of which were proteins and relatively easy to identify. However, the remaining four—all of which now appear to be miRNAs, including *bantam* and *mir14*—were initially intractable, says Hay.

He points out that the irony of this story is that the power of genetic screens is to let the organism tell you what is important and to show you novel things. Of course the team knew about miRNAs in *C. elegans*, but four years ago, they were still "stuck inside the protein box" and didn't seriously consider the possibility that their intractable mutants might be noncoding RNAs. That is, not until RNA silencing and miRNAs became a more familiar concept. "If there is a lesson to be learned," says Hay, "it is to listen harder to what your screens are trying to tell you. This one did exactly what it was supposed to do, we just weren't listening as closely as we should have been." ■

References: Brennecke, J., et al. 2003. *Cell.* 113:25–36.
Xu, P., et al. 2003. *Curr. Biol.* 10.1016/S0960982203002501.

Shared amyloid oligomer structure proves toxic

It was previously thought that the toxicity of Aβ and other amyloids resulted from large insoluble fibrils, but recently researchers have found that smaller soluble intermediates are cytotoxic. Now, Rakez Kayed, Elizabeth Head, Charles Glabe (University of California, Irvine, CA), and colleagues show that all of the soluble amyloid oligomers tested share a similar structure, and therefore also likely share a common mechanism of pathogenesis.



Kayed/AAAS

Preincubation of the antibody with oligomers (open bars) protected cells, whereas absence of antibodies and control antibodies had no effect.

Numerous degenerative diseases show evidence of amyloid formation. When the Irvine team raised antibodies against soluble Aβ oligomers, they obtained a highly specific antibody that binds to antigens based on structure, not amino acid sequence. The antibody binds to Aβ oligomers, but not to Aβ monomers or fibrils, or to the natively folded amyloid precursor protein. It also binds strongly and specifically to oligomers formed by numerous other amyloid proteins, including α-synuclein, islet amyloid polypeptide, polyglutamine, human insulin, lysozyme, and prion peptide 106–126. Preincubation of the antibody with any of these oligomers blocks their cytotoxicity.

"One of the real canons of biochemistry is that structure determines function. So if they all have the same structure, then they must all have a similar function, and all be doing something similar that is bad," says Glabe. Yet, many of the proposed mechanisms make sense for only one of the numerous amyloid diseases, which rules them out in Glabe's view. The real twist, he says, is that about half of the proteins act extracellularly and half intracellularly, leaving pretty much only the plasma membrane as a shared target. ■

Reference: Kayed, R., et al. 2003. *Science.* 300:486–489.