Use It or Lose It

A PROTEIN HELPS TUNE NERVES TO THE ENVIRONMENT BY KILLING OFF INACTIVE CELLS IN THE NOSE.

For a newborn mouse pup, some smells are critical to survival: milk, mom, bedding. As the pup grows older, the critical smells change to predator, food source, and mate. Over time, a mouse’s olfactory system becomes more adept at detecting the odors that matter. HHMI investigator Catherine Dulac of Harvard University has uncovered a small molecule that plays a big role in this process.

Each odor-sensing nerve cell, or neuron, in a mammal’s nose is specialized to detect a single type of smell. Because a typical mammal has about 1,000 odorant receptors, a fraction of which are needed at any one time, Dulac hypothesized that an animal might be able to “tune” its olfactory system to the environment by choosing which receptor to express at a given time.

Dulac and research associate Stephen Santoro found that olfactory neurons containing a protein called H2BE die sooner than neurons without the protein. H2BE is closely related to H2B, a so-called histone—a protein that helps organize DNA into compact forms that fit inside a cell’s nucleus and participate in regulating gene expression. Furthermore, as the team reported in the journal eLife on December 13, 2012, H2BE levels are inversely related to how active a cell is. Neurons with receptors that are constantly stimulated by smells have lower H2BE levels and thus live longer.

H2BE, they discovered, was replacing H2B in inactive neurons. “Slowly but surely, the genomes of neurons that are not stimulated by smells have lower H2BE levels and thus live longer. Neurons for rarely occurring smells—for example, mother’s milk once a pup matures—have a limited lifespan.

There are still many uncharacterized histone-like molecules in the brain, and Dulac believes that this novel system of regulation may be applicable to other brain functions. —Nicole Kruesi

IN BRIEF

brain chemicals, known as neuromodulators, to coordinate their reproductive behaviors.

Bargmann and her lab group at the Rockefeller University found a molecule in the worm Caenorhabditis elegans that is chemically similar to vasopressin and oxytocin—neuromodulators involved in mammalian reproductive behavior. Dubbed nematocin, the worm peptide binds to receptors in nerves and muscles and plays a role in coordinating complex behaviors. When Bargmann’s team created male worms lacking nematocin, the worms spent less time looking for mates. And when they encountered a partner, only a fraction of the nematocin-deficient males were able to complete the mating process. The group published the findings October 26, 2012, in Science.

That worms and mammals use similar neuromodulators suggests that a nematocin-like molecule has been conserved in animal nervous systems since worms separated from vertebrates about 600 million years ago. Next, Bargmann plans to figure out how the neuromodulator regulates behavior and then trace the evolution of that regulation.

OPPOSING NUCLEOTIDES

Several years ago, scientists in the laboratory of HHMI investigator Nathaniel Heintz discovered high levels of an unusual molecule called 5-hydroxymethylcytosine, or 5hmC, in brain cells. Its function was unknown, but new research by Heintz and his colleagues hints that it may play a role in the neurological disorder Rett syndrome.

5hmC is a modified form of cytosine—one of the four DNA building blocks. Intrigued by its abundance in brain cells, Heintz’s team at the Rockefeller University began mapping where the nucleotide occurred in the genome. They also identified locations of another modified version of cytosine, 5-methylcytosine, or 5mC. The resulting map revealed that 5hmC was most plentiful in active genes, while large amounts of 5mC appeared in inactive, or silent, genes.

A search for molecules that bind to 5mC turned up only one candidate—MeCP2, a regulatory protein that is mutated in Rett syndrome. As the team reported December 21, 2012, in Cell, tests showed that MeCP2 binds 5hmC and 5mC with equal affinity and that binding to 5hmC is associated with active transcription.

Heintz hypothesizes that the two modified forms of cytosine are responsible for different aspects of the disease. He plans to investigate how the same MeCP2 protein can trigger these opposing effects, depending on which nucleotide it binds.

THE SECRET TO (WORM) LONGEVITY

Schistosomes are parasitic flatworms that burrow through human skin and lay eggs that eventually lodge in major organs. As if that isn’t bad enough, the worms thrive in their hosts for decades. A discovery by HHMI investigator Phillip Newmark may help shorten this parasite’s lifespan.

Newmark studies planarians, relatives of schistosomes, in his laboratory at the Image