The Very Hungry Mouse

Activating One Set of Neurons Makes a Mouse Eat, and Eat, and Eat.

Within minutes of the activation of specific neurons in a mouse’s brain, the animal heads straight for its food dish. Despite the fact that the mouse is well fed and it’s not mealtime, it eats voraciously, as if starved. The mouse continues overeating until scientists turn off the neurons.

For Scott Sternson, a group leader at HHMI’s Janelia Farm Research Campus, this display is proof that a single group of neurons can modulate a complex behavior. Previous research suggested that feeding habits might be strongly affected by one neuron type, called agouti-related peptide (AGRP) neurons. When AGRP or a related molecule is injected into the brain of a mouse, it eats more. But the neurons had never been activated directly.

Sternson and his team relied on optogenetics, the use of light to activate neurons. They engineered AGRP neurons in mice to fire when illuminated by blue light from an optical fiber. When researchers switched on the light, the mice ate—more than 20 times the usual meal. The more neurons that were activated, the more the mice ate. When the light was quenched, the mice stopped eating.

It was thought that activating another neuron type, called POMC neurons, would have the opposite effect—that is, activating them would cause mice to eat less. Indeed, when Sternson’s team activated POMC neurons optogenetically, mice ate 40 percent less and lost 7 percent of their body weight in one day. This effect was abolished in mice with blocked melanocortin receptors, a key target of POMC neurons.

The researchers decided to tease apart the effects of POMC and AGRP neurons. “We wanted to know if the AGRP neurons were activating feeding by suppressing melanocortin receptor signaling,” says Sternson. So his team blocked this output of POMC neurons and then activated the AGRP neurons. The mice still raced to their food, the researchers reported in Nature Neuroscience in March 2011, showing that AGRP neurons are not acting through melanocortin receptors.

Sternson’s next goal is to identify the downstream neuron populations that AGRP neurons work through and construct a full circuit in the brain that controls eating behavior. —Sarah C.P. Williams

**In Brief**

Transcription begins when double-stranded DNA unwinds to expose its strands. Then the RNA polymerase (RNAP) enzyme attaches to the DNA and works its way along a gene sequence, producing a complementary strand of RNA as it moves. When it reaches the end of a gene, RNAP removes itself and releases the new RNA strand.

This process doesn’t always go smoothly, according to recent research: the RNAP can pause, restart, and even launch in the wrong direction. A research team led by HHMI investigator Jonathan S. Weissman of the University of California, San Francisco, found a way to study these bumps in transcription using a technique they call native elongating transcript sequencing (NET-seq). Once they’ve frozen the cell, stopping all activity, researchers can purify RNA strands mid-transcription. The sequences of the “frozen” strands tell them how transcription is progressing.

The team found instances of transcription happening in the wrong direction, but the process appeared to be actively discouraged by the cell. They also found specific places on the DNA where RNAP is most likely to stop and restart. The researchers are confident that their technique, described January 20, 2011, in Nature will reveal more about transcription and other cellular activities.

**What Sets Cancer Cells Apart**

Research by an HHMI-funded medical student has revealed that cancer cells display two important proteins recognized by the immune system. One tells the immune system not to attack and the other gives it a go-ahead. If scientists turn off the first protein, the immune system’s macrophages will destroy the cancer cells.

Mark Chao did the work at Stanford University while participating in HHMI’s Medical Research Fellows Program. In earlier research, Stanford’s Irving Weissman and Ravindra Majeti showed that macrophages attack cancer cells only if a surface protein called CD47 is blocked. CD47 is also present in normal cells, but blocking CD47 in those cells isn’t enough to get macrophages to attack. So researchers thought cancer cells must possess an additional protein that lets the body know they’re invaders. They suspected a protein called calreticulin.

Chao worked with Weissman and Majeti to show that calreticulin is expressed on the surface of many types of human cancer cells but not on the surface of normal cells. Furthermore, calreticulin was required for macrophages to recognize cancer cells and eliminate them. When calreticulin and CD47 are blocked, cancer cells are no longer destroyed.

Reporting their findings in the December 22, 2011, issue of Science Translational Medicine, the researchers also note that calreticulin is expressed more highly in cancers with worse clinical outcomes. The higher level of protein, unfortunately, isn’t enough to overcome the block that CD47 puts in place. But a therapeutic aimed at CD47 could get the job done.

**A Positive Finding for Triple-Negative Cancer**

New research reveals the genetic underpinnings of some cases of aggressive breast cancer. Triple-negative tumors are so named because they fail to test positive for any of the three traits that can be targeted by current drugs. HHMI investigator Steve Elledge has shown that in many of these cases a molecule called a tyrosine phosphatase is mutated.

Elledge’s team at Harvard Medical School used a genetic screen of triple-negative tumor cells to zero in on the phosphatase. An enzyme called PTPN12 is responsible for impeding the activity of a class of tumor-causing tyrosine kinases.