

## A Mutation's Multiple Effects

THE MUTATION THAT CAUSES A MOTOR NEURON DEGENERATIVE DISEASE ALSO PRODUCES DEFECTS IN BASIC CELLULAR MACHINERY.

Spinal muscular atrophy—a degeneration of motor neurons that causes muscle wasting—stems from mutations in a protein called “survival of motor neurons” (SMN). SMN does more than just keep motor neurons alive and functioning; it is vital in every cell in the body for splicing unneeded genetic bits out of RNA after it is copied from its DNA blueprint. SMN’s task is to construct small RNA-protein complexes, known as small nuclear RNA ribonucleoproteins (snRNPs)—the building blocks of the cell’s splicing apparatus (the “spliceosome”).

Since all cells need this housekeeping activity, it’s been a mystery why mutations in SMN affect only motor neurons. Now, researchers have discovered clues to the mechanism that allows the

mutation to have varied responses in different tissues.

When they engineered cultured human cells with reduced SMN levels, researchers led by HHMI investigator Gideon Dreyfuss of

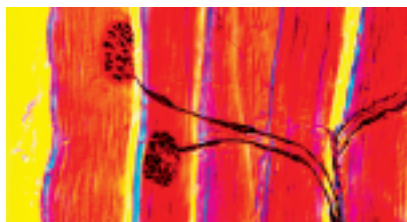
the University of Pennsylvania School of Medicine found that not all the snRNPs were affected in the same way. “Rather than a uniform decrease in the levels of all the snRNPs, some were more affected than others,” says Dreyfuss.

To explore whether this varied response might affect tissues in different ways, the researchers turned to SMN-deficient mice.

“We found a different snRNP repertoire change in every tissue we looked at,” says Dreyfuss.

When the scientists looked at how RNA was spliced in these mice, they also found tissue differences. “The abnormalities we saw told us clearly there is something aberrant about the splicing process,” explains Dreyfuss. “Not only did we see basic splicing defects, we also saw spliced RNA forms never before detected in normal mice in any tissue.”

The results, which appear in the May 16, 2008, issue of *Cell*, don’t answer why motor neurons are affected so drastically, but they do reveal that SMN is a key orchestrator of the splicing process and illustrate how different tissues respond in a unique way to mutations in a protein needed by all. Knowing that patients with spinal muscular atrophy have spliceosome defects in more than just neural cells, Dreyfuss says, suggests that future therapies should target the whole body. ■ —SARAH C.P. WILLIAMS



Spinal muscular atrophy causes motor neurons, shown here as they connect to skeletal muscle, to degenerate.

### IN BRIEF

#### TOXIC RNA IN NEURODEGENERATION

The explanation for one neurodegenerative disease just got more complex. Mutated RNA, which folds back on itself in a hairpin, is partially to blame for the loss of motor control associated with spinocerebellar ataxia type 3 (SCA3), according to a study by HHMI investigator Nancy M. Bonini. Previously, scientists believed the symptoms of SCA3 were due only to an accumulation of irregular, toxic proteins.

Bonini, at the University of Pennsylvania, generated a fruit fly model of SCA3—which is caused by a long string of repeated nucleotides inserted in a gene. After two genetic experiments hinted to Bonini that RNA might be involved, her team replaced the repeats of “CAG” nucleotide triplets with some “CAA” repeats. These triplets code for the same amino acid—and so the same protein in the end—but the “CAA” version didn’t make the RNA fold up. Toxicity decreased, despite the protein being identical. In addition, Bonini and her colleagues engineered flies that produced repetitive RNA but no protein. They still saw neural degeneration, they reported in *Nature* on June 19, 2008.

“There’s toxicity at the level of the protein, but also at the level of the RNA,” says Bonini. “We would argue that, thera-

peutically, this means knocking down the RNA to prevent expression of the toxic protein is really a two-pronged approach—you get rid of both toxicities.”

#### CANCER'S ELUSIVE STEM CELLS

A protein that researchers once believed flagged only colon cancer stem cells—hypothesized to be the seeds that keep a tumor growing—has now been shown to be far more common. The new research, by HHMI investigator Shahin Rafii and his colleagues at Cornell University, casts doubt on the very idea that cancer stem cells exist.

Since the 1960s, researchers have been aware that not all cancer cells can cause cancer. So when scientists pinpointed a protein—CD133—that seemed to exist only in a small percentage of colon cancer cells, they guessed that it could be unique to stem cells—a cancer stem cell marker. But Rafii looked closer at the protein’s localization.

Instead of injecting human colon cancer cells into mice, Rafii used mice with a mouse version of colon cancer. And instead of staining segments of tissue to locate CD133, as others have done, Rafii and his colleagues used a genetic method to track the protein.

What they found surprised them. “It’s all over the place, in every epithelial lining you

can think of—the lung, pancreas, brain, colon,” says Rafii. “If you have a marker expressed on all these mature cells, then it’s hard to conclude that CD133 is a stem cell marker.”

In addition, by growing cancer cells that expressed CD133 as well as ones that didn’t, Rafii showed that some of each could initiate new cancers. The research appears in the June 2, 2008, issue of *The Journal of Clinical Investigation*.

While cancer stem cells could exist, Rafii says his findings emphasize how hard it is to find them. “We need a functional definition of a cancer stem cell rather than a marker,” he says.

#### EXPOSING A PARASITE'S VULNERABILITY

Like the words in a sentence, the order of amino acids in a protein is typically vital to its meaning. But one malaria parasite, researchers have shown, can recognize proteins whose amino acids are randomly scrambled—as long as the whole protein still has certain characteristics.

Led by HHMI international research scholars Geoffrey McFadden at the University of Melbourne and Alan Cowman at the Walter and Eliza Hall Institute of Medical Research—both in Australia—the scientists wanted to find out the required