

Compensatory Tactics

Experiments with “sticky” mice show that cells can use modifier genes to sidestep a mutation’s adverse effects.



“By working on these compensatory aspects of a disease... you may be able to stop or slow its progression. ”

SUSAN ACKERMAN

The power of mouse genetics provides Susan Ackerman a whole new view of the mechanisms behind neurodegeneration.

Paul Fetters

WITH ITS ROUGH, MATTED FUR AND PINT-SIZED FRAME, THE MOUSE STRAIN known as “sticky” was destined for genetic study. Thus, a colony with the *sti* mutation, which spontaneously arose in a University of Cambridge lab around 1984, was transferred to The Jackson Laboratory in Maine, to produce a line for dermatologic research. There, a sharp-eyed research assistant noticed that, over time, the sticky strain developed additional, more disturbing traits: Starting with mild tremors in their limbs, the animals began losing muscle control, ultimately having difficulty walking or even moving.

Studies later showed that the aging mice gradually lost Purkinje cells in the cerebellar cortex, the part of the brain responsible for motor control and balance. That’s when HHMI investigator Susan L. Ackerman entered the picture.

A geneticist at The Jackson Laboratory, Ackerman uses a “forward genetics” approach, starting with an organism’s outward physical traits—or phenotype—and working back to identify the mutated gene. “Even as an undergraduate, I loved the idea of having a mutation in a gene that causes some sort of phenotype, and then trying to fill in the gaps between A and Z,” she says. This strategy served her well in 1997, when she linked defects in developing brains to a gene critical to cell migration and axonal guidance. In 2002, her study of a mutant mouse called *harlequin* surprised the scientific community by revealing that a gene long thought to play a critical role in promoting neuron death actually functioned to keep nerve cells alive.

In her first study of the *sticky* mouse, Ackerman traced the *sti* mutation to a gene called *Aars*, which encodes an enzyme involved with attaching the correct amino acids to a transfer RNA (tRNA) during protein synthesis. Normally, these enzymes have “editing” domains that make sure the correct amino acid is loaded (or “charged”) onto its carrier tRNA. Ackerman’s research revealed that *sticky* mutants were defective in their ability to edit mischarged tRNA, resulting in a deadly buildup of misfolded proteins in brain cells. Her findings appeared in the September 7, 2006, issue of *Nature*.

These types of editing errors have yet to be linked to any human neurodegenerative

disease, but Ackerman says the similarity between mouse and human genomes makes it highly likely that similar genetic mishaps can lead to neurodegeneration in aging humans.

In a follow-up study, Ackerman crossed *sticky* mutants with other mouse strains to see if the neurodegenerative effects would appear in mice with different genetic backgrounds. Previous studies had shown that when a mutated gene is crossed into a different strain of mouse, the characteristic traits of the mutation sometimes disappear. In such cases, the actions of other genes, called “modifier” genes, can create alternatives, such as compensatory pathways, that allow cells to deal with the cumulative damage a mutation causes.

That is indeed what happened when Ackerman crossed *sticky* mice with other strains. Though all the resultant mice carried a copy of the *sti* mutation, most of them scampered into old age unimpaired by motor dysfunction.

That study and others provided Ackerman with a starting point from which to track modifier genes associated with the accumulation of misfolded proteins in neurons that can trigger cell death. Recently, the Ackerman team identified a gene that works to suppress neurodegeneration in *sticky* mice. Though *sticky* mice normally begin losing Purkinje cells at 3 to 4 weeks of age, preliminary studies reveal that mice with the suppressor gene maintain motor function at 12 months of age. Brain tissue samples show that, although some Purkinje cell loss occurs, most of the neurons survive.

How do these cells persevere? Ackerman theorizes that the modifier gene works to prevent the accumulation of misfolded proteins by enhancing the Purkinje cells’ ability to get rid of them.

Ackerman says that knowledge of how modifier genes work to prevent such damage may present new therapeutic options for treating diseases caused by protein misfolding. For example, a modifier gene that creates a pathway to prevent cumulative damage in the cell could be chemically activated to speed up the mechanism for damage control.

“By working on these compensatory aspects of a disease, even though you haven’t fixed the primary cause, you may be able to stop or slow its progression,” she says, “and that would be enormously helpful.” ■

– SUSAN GAIDOS

Tempering Oxidative Stress

Ackerman is also using modifier genes to suppress oxidative stress in the brain, which has been linked to diseases such as Alzheimer’s, Parkinson’s, and amyotrophic lateral sclerosis, or “Lou Gehrig’s disease.” Oxidative stress occurs when chemicals called free radicals accumulate in a cell and damage proteins, DNA, and other cellular components. Recently, Ackerman’s lab identified a gene that, when mutated in mice, results in high levels of oxidative stress throughout the brain. Mice with this genetic mutation develop motor problems associated with neuron loss soon after birth and die around six weeks of age.

She has also identified a modifier gene that, when placed in the mutant mice, reduces the neuronal damage caused by oxidative stress. Through a breeding process called backcrossing, Ackerman transferred the modifier gene into a group of mutant mice. Preliminary studies show that those with the modifier gene are able to sidestep the most severe aspects of the disorder and live longer—more than two years. In addition, the mice develop the first symptoms of disease much later in life.