Drug response depends on mouse substrain

Researchers have found that a single nucleotide polymorphism (SNP) causes a disparity in drug responses between two substrains of the C57BL/6 inbred laboratory mouse. The finding points to the care that must be taken when comparing behavioral data from mice of difference substrains.

The research mouse strain C57BL/6J has been maintained at the Jackson Laboratory since 1948. In 1951, a colony of these mice was sent to the National Institutes of Health, and C57BL/6N became a second major source of C57BL/6 mice. Because of genetic drift over nearly a century, populations of C57BL/6 mice have developed into at least 20 substrains. Although behavioral differences have been noted in C57BL/6 substrains, their genetic basis has not been elucidated.

A team led by Joseph Takahashi (University of Texas Southwestern Medical Center and Howard Hughes Medical Institute, Dallas, TX) compared the locomotor response to cocaine and methamphetamine in C57BL/6J mice and C57BL/6N mice. C57BL/6N mice had a 45% lower acute response to both drugs

Ted Foxx / Alamy

at multiple doses and sensitized to cocaine much less efficiently than the C57BL/6J strain (*Science* **342**, 1508–1512; 2013). "They are clearly not interchangeable," says Gary Churchill, one of the study's authors.

They further demonstrated that C57BL/6N mice have a lower number of total dendritic spines on the medium spiny neurons in the nucleus accumbens; these cells play an important role in drug addiction.

To find out if SNPs accumulated through genetic drift could account for the phenotypic difference, the scientists carry out quantitative trait locus analysis. They were able to map the genetic difference between the strains that was associated with the drug response to a single locus on a 22-Mb interval between 35 Mb and 57 Mb of chromosome 11. Whole-genome sequencing further uncovered a SNP within that interval producing a missense mutation in *Cyfip2*. This gene encodes a highly conserved protein that is widely expressed throughout the brain. The SNP destabilizes the structure of CYFIP2, though the scientists could not pinpoint an alteration in the protein's function. Still, they confirmed the importance of the protein in regulating the response to drugs by generating mice with the *Cyfip2* mutation; these mice showed acute and sensitized responses to drug administration similar to the C57BL/6N mice.

They further estimated that the *Cyfip2* polymorphism was fixed in the C57BL/6N genome sometime between 1961 and 1974 and is present in the most commercially available sources of the strain, including those from Charles River Laboratories and Taconic.

Kara Rosania

CELL COMMUNICATION FEEDS THE FOUNTAIN OF YOUTH

Aging can be broadly defined as a gradual decline in function over time; it is one of the most conserved features of living organisms. Mitochondrial dysfunction is a hallmark of aging, but the mechanisms contributing to the disruption of mitochondrial homeostasis are not clearly understood. Now, researchers led by David Sinclair (Harvard Medical School, Boston, MA) report that a disruption of intracellular communication between the mitochondria and nucleus contributes to aging-related mitochondrial dysfunction.

Nuclear–mitochondrial communication is key, as different subunits of the energy-producing oxidative phosphorylation (OXPHOS) system are encoded in the two genomes; failure to coordinate the two impairs the cell's energy supply. Sinclair's group noted that in aging mice, activity of only the mitochondrially encoded components of the OXPHOS system declined (*Cell* **155**, 1624–1638; 2013).

As their search to identify the biochemical underpinnings of this decline progressed, they investigated several molecules known to be associated with aging or lifespan extension. NAD^+ is a coenzyme involved in energy production whose concentration declines with age. It controls the activity of SIRT1, an enzyme with an established role in lifespan extension. Sinclair's team next carried out a series of experiments using aging and *Sirt1*-knockout mice.

When taken together, the experimental results suggest that as the concentration of NAD^+ in the nucleus falls with age, SIRT1 activity is reduced, allowing the transcription factor HIF-1a to accumulate. Accumulation of HIF-1a interferes with normal nuclear–mitochondrial communication, leading to declines in mitochondrial OXPHOS subunits and disruption of mitochondrial homeostasis.

Finally, Sinclair's group evaluated whether they could prevent the disruption, restore intracellular communication and, in effect, turn back the hands of time. They administered a precursor of NAD^+ to aging mice for 1 week and observed increases in mitochondrial OXPHOS subunits along with reversal of biochemical changes related to aging. After the 1-week treatment period, mice that were 22 months old had health biomarkers (including indicators of insulin resistance, inflammation and muscle wasting) similar to those normally seen in 6-month-old mice. A similar improvement in humans might be a 60-year-old person with muscle tissue of a 20-year-old, according to the researchers. "There's clearly much more work to be done here, but if these results stand, then certain aspects of aging may be reversible if caught early," said Sinclair in a statement.

Future studies will analyze longer-term outcomes of NAD^+ precursor administration, as well as potential applications in treating rare mitochondrial and more common metabolic diseases, such as diabetes.

Monica Harrington