

JANUARY 27, 2006

Making Mice Old Before Their Time

Knocking out a gene that helps repair nicks in DNA causes young mice to develop many of the degenerative characteristics of their wizened elders. Mice lacking the gene develop hunchback, thinning skin, decreasing bone density, and a declining immune system -- all in the span of a month.

The researchers do not know whether the accelerated aging-like effects of losing the gene, called *SIRT6*, relate to its role in DNA repair. Nor do they know whether the degenerative effects are relevant to the natural aging process. However, they said, the discovery offers an intriguing new model for studying DNA repair, as well as its possible role in aging-related degeneration.

The researchers, led by Howard Hughes Medical Institute investigator Frederick W. Alt, reported their findings in the January 27, 2006, issue of the journal *Cell*. First authors of the paper were Raul Mostoslavsky, Katrin Chua and David Lombard in Alt's laboratory at The Children's Hospital Boston, CBR Institute for Biomedical Research and Harvard Medical School. Other co-authors were from Brigham and Women's Hospital in Boston, Harvard School of Public Health, MIT, Tufts University School of Veterinary Medicine, the National Cancer Institute, and the University of Zurich in Switzerland.

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- **Frederick W. Alt**

The research on *SIRT6* is part of a broad effort in the Alt laboratory to study the role of a family of seven known mammalian sirtuin genes. These studies were prompted by findings some two decades ago that a yeast counterpart called *Sir2* maintains genomic stability and regulates aging in yeast cells. Researchers had also found that enhancing the activity of *Sir2*'s counterparts in the roundworm and fruit fly extended their life span.

Alt and his colleagues were particularly interested in the sirtuin genes because of the yeast *Sir2*'s role in maintaining chromatin -- the complex of DNA and protein that makes up chromosomes.

“While we've been exploring the effects of knocking out each of the sirtuin genes, we've found that the *SIRT6* knockout produces the most dramatic effects,” he said. In their experiments, Alt and his colleagues explored the effects of knocking out *SIRT6* at both the cellular and whole-animal levels.

Their analyses of mouse cells lacking the gene showed a fundamental genomic instability. For example, the cells were particularly sensitive to chemicals known to react oxidatively with DNA, such as hydrogen peroxide. Working with co-author Bruce Demple and his colleagues at the Harvard School of Public Health, the researchers found that the *SIRT6*-deficient cells were defective in the cell's primary repair mechanism to correct the type of DNA damage generated by these oxidative chemicals. This process, called base excision repair (BER), involves detecting and replacing incorrect or damaged DNA on one strand of the double-stranded molecule.

When the researchers expanded their experiments to produce mice lacking the gene, they saw more dramatic results. “These animals appear fine when they're born, although they are somewhat smaller than normal,” said Alt. “But at three weeks of age they go into a decline due to a number of abnormalities that overlap with aging-associated degenerative processes.” These abnormalities include loss of white blood cells that leads to a compromised immune system; a spinal hunchback; lowered bone mineral density, and a profound drop in blood glucose that reaches negligible levels by the time the animals die at about one month of age.

“Although these kinds of abnormalities are interesting in that they correlate with those seen in aging, they could be due to some other mechanism entirely,” said Alt.

Alt said that while *SIRT6*-deficiency is a good model for studying base excision repair at the cellular level, its value as an animal model remains unknown. “We have a lot more work to do to confirm the value of the model in whole animals,” he said. “We have seen defective BER in two types of cells in such mice, but we don't know that this repair process is defective in every tissue. At this point, we can't conclude that all of the effects we see in the mice are due to defective BER. As we have found in our studies of *SIRT1*, it's quite possible that *SIRT6* regulates more than one process or pathway.”

A mouse model of the potential effects of base excision repair on aging would be especially useful, said Alt, because other known mutations that affect base excision repair are either lethal or have no obvious effect. Thus, Alt and his colleagues are working toward establishing the value of a *SIRT6*-knockout mouse model of base excision repair. For example, they are testing the effects of knocking out *SIRT6* only in specific tissues of the mice,

to distinguish the multitude of effects caused by a complete loss of the gene.

Alt said while it would be premature to speculate on the clinical value of drugs that could affect *SIRT6*, “it is certainly of interest, because, in addition to base excision repair, *SIRT6* is clearly linked to metabolic processes, and it could be of clinical importance for that reason.”