Extending healthy life through gene manipulation: Sounds cool but it's complicated

Over and over, the same theme has been emerging regarding the ability to understand and if desired manipulate genes that explain the genetic basis of various phenomena in biology. We've seen this with the flurry of news and excitement focused on the genetics of athletic ability, effects of diets, personality and a range of diseases and behaviors.

The same is true when it comes to lifespan, but with an added dimension. It's not just the duration of life that we want to extend; it's also the youthful, healthy period. While researchers in aging recently discovered that extending the lifespan of nematode worms (*Caenorhabditis elegans*) does not increase the period of youth and health, the finding should not be thought of as a setback. Instead, it launches longevity research into a new phase in which scientists will hone in on genetic factors that, when harnessed, could allow older people to function more as younger people do today.

Science of aging maturing with age

Beginning in the 1990s, nematode studies led to a great deal of excitement. By manipulating just a few genes, researchers were able to extend the lifespan of the worms up to five fold. In the years that followed, this milestone was described as the equivalent of a human living 400-500 years and it was thought that an extended period of youth and vigor accounted for much of the increased lifespan. But a study, conducted at the University of Massachusetts, tells a very different story. Assessing aging by looking at a variety of traits, the UMass research suggests that nematode lifespans extended by manipulation of the aging genes actually is not dominated by a long, healthy, youthful period.

"While we saw some extension in health as the mutants aged for certain traits, invariably the trade-off was an extended period of frailty and inactivity for the animal," says principal investigator of the UMass study, Heidi Tissenbaum. Different from previous studies that looked at only a couple of traits associated with nematode health, Tissenbaum's team identified a variety of traits, and used them to define what they term a "healthspan", which must be distinguished from lifespan.

Rather than being discouraging, the finding should push longevity research into a new direction, where scientists can begin honing in on the genes that extend health in association with lifespan extension.

"If we want to find the genes that help us remain physically active as we age, the genes that will allow us to play tennis when we're 70 similar to when we were 40, we have to look beyond longevity as the sole criteria," notes Tissenbaum, a professor of molecular, cellular and cancer biology, and of the UMass program in molecular medicine.

Advances outside the world of nematodes

Nematodes have been used a great deal in aging research, because they're among the simplest of multicellular organisms. However, recent times have produced several encouraging achievements in life

extension research involving other animals. One example is the Methuselah fly. Naming their test animal for the character of Hebrew mythology who lived more than 900 years, investigators at the University of Bern, in Switzerland, recently succeeded in extending the lifespan of *Drosophila melanogaster* flies by 50-60 percent. It's not totally clear yet whether the time added to the *D. melanogaster* lifespan was dominated by an extended period of health. However, the immediate effects of the genetic manipulation that the Swiss researchers employed suggests that extended health should be the reason for the lifespan increase.

Known as *azot*, the altered gene in the Swiss technique causes efficient elimination of bad or aging cells throughout a fly's life. At the same time, healthy cells are maintained to support body tissues. In other words, *azot* is an enhanced quality control gene, and improved quality control over a lifetime should mean better health. Also, since the *azot* gene is conserved in humans, the fly study suggests that an analogous human effect may be possible.

Another new study, this one involving mice at Brown University, also has revealed an aging-relevant gene. It's known as the *Myc* gene, and when its activity is reduced the mouse lifespan is extended by 15 percent. Moreover, unlike all other longevity models involving mammals, various health issues commonly associated with both mouse and human aging are reduced in association with the lifespan increase. Specifically, the Brown study showed reduction in osteoporosis, immunity problems, and cardiac fibrosis in those mice with decreased *Myc* activity.

"These mice are incredibly normal, yet they are really long-lived," says John Sedivy, senior author on the study, who emphasizes an important point: "In many other longevity models like caloric restriction or treatment with rapamycin, the animals live longer but they also have some health issues."

Moving up the ladder from small to larger animals brings us the recently published results on the genome of bowhead whales. These animals can have lifespans approaching 200 years and a study has identified some 80 genes that we may be able to use, adapt, or otherwise apply to humans. While we're not likely to acquire the ability to dive underwater with no equipment for hours at a time, the hope is that this, and the various studies involving other species, will lead us to an age when a whale might look out from the water to a distant shore and spot a group of century-old humans running along the beach the way they would at age twenty.

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