



## In the quest to stymie time, will laboratory data stand up in man?

Age is the greatest risk factor for developing a neurodegenerative disease; it robs us of our hearing and bone mass and is correlated with myriad other declines in organ and sensory function. As the average lifespan increases and the aging population grows, the search for a fountain of youth is more determined than ever.

But while it is agreed that multiple, seemingly stochastic processes drive aging, the underlying mechanisms are vague. There are so many theories on aging that it's hard to keep track. Did Leonard Hayflick hit the nail of senescence on the head when he proposed that our cells can divide a limited number of times, after which they die? Or is chronic inflammation the answer to the aging conundrum? Maybe the accumulation of free radicals or genetic mutations or telomere erosion causes the wear and tear we face as years pass.

"One of the problems in determining the mechanisms of aging is that aging is such a complex process," said Lawrence Donehower, a professor at Baylor College of Medicine. "Unlike some diseases that may affect a given cell type and be specific in origin, aging affects all organs in different ways, it differs substantially among individuals, is affected by diet, behavior, and environment in different ways, and is affected by the presence or absence of non-aging- and aging-associated diseases."

Donehower explained that until about 10 years ago, the lack of a significant genetic underpinning restricted what could be learned mechanistically about aging, and what was known seemed descriptive and phenomenological. It wasn't until the discovery in worms and flies, and then mice, that mutations in some genes could enhance or reduce longevity, that we had a grasp of which cellular pathways and processes were important in aging.

"The realization that aging can be retarded by discrete genetic manipulations in single genes is a rather new one, and the field of molecular gerontology has progressed very rapidly in the last 10 years," said Thomas Nyström of Göteborg University.

But results from the lab don't necessarily translate into increased longevity in humans. Caloric restriction has been shown to extend the average lifespan in rodents and other species, but the effects



Staying young. Scientists are trying harder than ever to retard the aging process and understand its underlying mechanisms, but will results in laboratory animals apply to humans? Photo courtesy of the NIH.

on humans are speculative. Likewise, many studies have reported disrupted melatonin production and circadian rhythms in aging, and although some groups have reported positive results with light therapy and melatonin supplements, there is no evidence that melatonin increases human longevity. Hormone therapy and antioxidant use also look promising in laboratory data.

And now there are 2 new sets of findings to add to our arsenal of age-defying defenses. Researchers have found that adult mice lacking a tumor suppressor-related gene called p63 in targeted tissues aged prematurely with all the signs we are familiar with — hair loss, spine curvature, and reduced physical fitness (1).

Premature aging was previously seen in mice lacking a hormone called Klotho. Now, the same team responsible for that work has made mice that overexpress the hormone (2), which live 19–31 percent longer than their normal littermates.

While Donald Ingram, acting chief of the Laboratory of Experimental Gerontology at the National Institute on Aging, said he has never been too awed over claims about accelerated aging, yet he is excited by demonstrations of decelerated aging and increased health and lifespan. "The recent paper on the Klotho-overexpressing mice has impressed me. They have identified a putative hormone that appears to increase lifespan and have linked it to a mechanism," he said.

Donehower agreed that the problem with model studies producing accelerated aging is that what you are looking at may not necessarily be aging, but some non-aging pathology. He says he was dubious about

the original Klotho knockout model but the new study has changed his mind. "I think Klotho is now vindicated as an aging gene by the report that overexpression of *klotho* in mice results in longevity extension. This is the gold standard for an aging-associated gene," he told the *JCI*.

Will results like this stand up in people? Nyström thinks that the substantial effects of manipulations seen in lab animals will be much less pronounced in more complex organisms, including man. "I expect the maximal potential extension of lifespan we can achieve in humans will be rather small compared to fungi, worms, and flies," he said. "And the trade-off may be a higher risk of cancer and/or reduced fitness."

In fact, the mechanism by which Klotho extends lifespan is the same as the way caloric restriction works — by increasing insulin resistance. Insulin resistance is a key symptom of diabetes, and Klotho also decreases fertility.

But scientists and the public remain hopeful that one day we will be able to extend longevity. Companies are already experimenting with drugs that boost aging-associated proteins such as Sir2, an enzyme that removes acetyl groups from proteins and which has been shown to increase lifespan in lower species. Like Donehower said, "I don't think it's a matter of if, but of when."

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1. Keyes, W.M., et al. 2005. p63 deficiency activates a program of cellular senescence and leads to accelerated aging. *Genes Dev.* doi:10.1101/gad.342305.
2. Kurosu, H., et al. 2005. Suppression of aging in mice by the hormone Klotho. *Science.* doi:10.1126/science.1112766.