

# Clinical Update

## **Natural Cancer-Fighting Protein May Also Slow Aging**

Mice with extra p53 lived longer, even after factoring in cancer deaths, study finds

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There's no fountain of youth waiting around the corner, but a study of unusually old mice suggests a natural anticancer protein might also put the brakes on aging.

The protein, called p53, along with one of its cellular regulators, called Arf, may boost the body's antioxidant activity to keep cells younger longer, according to research in the July 19 issue of *Nature*.

In the study, a team of cancer investigators closely examined cells from mice genetically engineered to produce extra amounts of p53 and/or Arf.

"When we examined markers of aging in these mice, we observed that their aging is slower," said senior researcher Manuel Serrano of the Spanish National Cancer Research Centre in Madrid. This extended lifespan wasn't just due to p53's well-known anti-cancer activity, he said, since aging was slowed even when the researchers took cancer suppression into account.

Cancer researchers are certainly no strangers to the p53 protein, which is produced naturally by the body.

"P53 is the undisputed 'star' in cancer research -- scientists know more about p53 than about any other gene or protein," Serrano said. That's because the protein helps target and eliminate what he called "unhappy" cells -- cells with broken DNA, or cells poorly supplied in oxygen -- that have a higher risk of becoming malignant.

"P53 kills the unhappy cells by activating another complex cascade of events (only partly understood) that includes self-digestive proteins that basically destroy the cell," Serrano explained.

P53 is helped in this task by the regulatory chemical Arf, which lets p53 know that a particular cell is in trouble and marked for elimination.

Throughout their years of work with p53/Arf, Serrano's Spanish team has utilized a genetically engineered strain of lab mice that produces extra-high quantities of the two proteins. The Madrid researchers noted that these rodents lived longer than other mice, even when the scientists factored out reductions in cancer-related death.

While no one is sure just how p53 keeps cells young, Serrano believes the protein "delays aging for exactly the same reason that it prevents cancer."

"In the aging field, everyone agrees that aging is produced by the accumulation of faulty cells," he said. However, p53/Arf appears to be a kind of "quality control" manager in this regard, eliminating bad cells that cause cancer and speed up the aging process. Therefore, "the



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expectation is that by having more p53, mice will have more strict quality control for cells, hence less cancer and less aging," Serrano said.

In fact, p53 may be a key to explaining why cancer incidence rises near the end of any mammal's lifespan, the researchers said. This sharp rise in malignancy isn't dependent on how many years the animal lives (for example, mice live about three years, humans close to 80). Instead, it always occurs near the end of a particular animal's expected lifespan.

So, "the fact that we have evolved to be such a long-lived species probably requires that we can fight cancer [longer]," and p53 probably helps humans do that, said Felipe Sierra, director of the Biology of Aging Program at the U.S. National Institute on Aging. He believes p53/Arf plays a key role in keeping cancer at bay throughout youth and middle-age, but this effect may wane in old age.

According to Sierra, the Spanish study helps answer the question of why aging and cancer are so closely intertwined, and p53's role in that relationship. "The fact that there was a connection was suspected for a long time, but it was difficult to prove," he said. "It's perfectly sensible that there's this correlation between these two things."

But don't look for any elixir of eternal life anytime soon, the experts said.

"There are a number of chemical compounds that have been developed by big pharmaceutical companies, and these compounds are able to boost p53 in the organism," Serrano noted. But testing of these compounds is still in its earliest stages and safely "fine-tuning" the p53 cascade will likely be a delicate process. "To achieve this fine-tuning with chemical drugs may not be that easy," he said.

Sierra was similarly cautious. "We're not really talking here about anything that can manipulate the system," he said. "This is just about basic mechanisms, so we can start looking in different directions. There's no fountain of youth in the near future."

