MedicalXpress

Male hormone reverses cell aging in clinical trial

July 26 2016

Telomerase, an enzyme naturally found in cells, is often described as a "cellular elixir of youth." In a recent study, Brazilian and U.S. researchers show that sex hormones can stimulate production of this enzyme.

The strategy was tested in patients with genetic diseases associated with mutations in the gene that codes for telomerase, such as aplastic anemia and pulmonary fibrosis. The authors say that the results suggest that the approach can combat the disease-related damage by telomerase deficiency.

The study was performed by Brazilian researchers in collaboration with colleagues at the National Institutes of Health (NIH) in the U.S. Among the scientists involved was Rodrigo Calado, a professor at the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP) and a member of the Center for Cell-Based Therapy (CTC), one of the Research, Innovation and Dissemination Centers (RIDCs) supported by FAPESP.

"One of the processes associated with aging is progressive shortening of telomeres, DNA-protecting structures at the ends of chromosomes, like the plastic tips on shoelaces," Calado said. "Each time a cell divides, its telomeres get shorter. Eventually, the cell can't replicate anymore and dies or becomes senescent. However, telomerase can keep the length of telomeres intact, even after cell division."

In practice, he added, telomere length is a laboratory measure of a cell's "age." Some cells avoid aging by using telomerase to lengthen their telomeres through the addition of DNA sequences, thereby maintaining their capacity to multiply and resist aging.

In an embryo, where tissue is still in the formative stage, telomerase is expressed by practically every cell. After the embryonic period, only cells that are constantly dividing, such as hematopoietic (blood-forming) stem cells, which can differentiate into a variety of specialized cells, continue to produce telomerase.

"Aplastic anemia is one of the diseases that can be caused by telomerase deficiency," Calado said. "Bone marrow stem cells age prematurely and fail to produce enough red blood cells, white blood cells and platelets, making the patient dependent on blood transfusions and more susceptible to infections."

In 2009, Calado and collaborators published an article in the journal *Blood* showing that androgens, which are converted into estrogens in humans, bind to female hormone receptors in the telomerase gene promoter region and thereby stimulate expression of the enzyme in cells.

"The study we've just published was designed to find out whether the effect we'd observed in the lab also occurred in humans, and the results indicate that it does," Calado said.

Instead of estrogen, the researchers treated the patients with androgen, he explained, because it has long been used as a drug in cases of congenital anemia and offers the advantage of stimulating an increase in the mass of hemoglobin (red blood cells), which estrogen cannot do.

Treatment with the steroid danazol, a synthetic male hormone, was tested for two years in 27 patients with aplastic anemia owing to

telomerase gene mutations.

"In a healthy adult, telomere length varies from 7,000 to 9,000 base pairs on average. A normal person's telomeres lose 50 to 60 base pairs per year, but a patient with telomerase deficiency can lose between 100 and 300 base pairs per year," Calado said. "In the patients who received danazol, telomere length increased by 386 base pairs on average over two years."

In addition, hemoglobin mass rose from 9 grams per deciliter (g/dL) to 11 g/dL on average. A person without anemia normally has between 12 and 16 g/dL, but the improvement observed in these subjects was sufficient to rid them of transfusion dependency.

"On completion of the protocol, the medication was interrupted, and we observed a fall in all counts. Several patients resumed the medication with smaller doses, individually adjusted to minimize side effects," Calado said.

In a new protocol currently in progress at the University of São Paulo's Ribeirao Preto Blood Center, the same kind of approach is being tested with nandrolone, an injectable male hormone.

Although the results of the study suggest that drugs can be used to reverse one of the biological drivers of aging, it is not yet clear whether the benefits of treatment would surpass the risks in healthy people, especially if the treatment involved the use of sex hormones.

Some groups, such as patients undergoing chemotherapy or radiotherapy, may benefit from drugs that stimulate telomerase in the future.

More information: Danielle M. Townsley et al, Danazol Treatment for Telomere Diseases, *New England Journal of Medicine* (2016). DOI:

10.1056/NEJMoa1515319