Scientists find a key to maintaining our DNA

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DNA contains all of the genetic instructions that make us who we are, and maintaining the integrity of our DNA over the course of a lifetime is a critical, yet complex part of the aging process. In an important, albeit early step forward, scientists have discovered how DNA maintenance is regulated, opening the door to interventions that may enhance the body's natural preservation of genetic information.

The new findings may help researchers delay the onset of aging and aging-related diseases by curbing the loss or damage of our genetic makeup, which makes us more susceptible to cancers and neurodegenerative diseases, such as Alzheimer's. Keeping our DNA intact longer into our later years could help eliminate the sickness and suffering that often goes hand-in-hand with old age.

"Our research is in the very early stages, but there is great potential here, with the capacity to change the human experience," said Robert Bambara, Ph.D., chair of the Department of Biochemistry and Biophysics at the University of Rochester Medical Center and leader of the research. "Just the very notion is inspiring."

In the Journal of Biological Chemistry, Bambara and colleagues report that a process called acetylation regulates the maintenance of our DNA. The team has discovered that acetylation determines the degree of fidelity of both DNA replication and repair.

The finding builds on past research, which established that as humans evolved, we created two routes for DNA replication and repair – a

standard route that eliminates some damage and a moderate amount of errors, and an elite route that eliminates the large majority of damage and errors from our DNA.

Only the small portion of our DNA that directs the creation of all the proteins we are made of – proteins in blood cells, heart cells, liver cells and so on – takes the elite route, which uses much more energy and so "costs" the body more. The remaining majority of our DNA, which is not responsible for creating proteins, takes the standard route, which requires fewer resources and moves more quickly.

But, scientists have never understood what controls which pathway a given piece of DNA would go down. Study authors found, that like a policeman directing traffic at a busy intersection, acetylation directs which proteins take which route, favoring the protection of DNA that creates proteins by shuttling them down the elite, more accurate course.

"If we found a way to improve the protection of DNA that guides protein production, basically boosting what our body already does to eliminate errors, it could help us live longer," said Lata Balakrishnan, Ph.D., postdoctoral research associate at the Medical Center, who helped lead the work. "A medication that would cause a small alteration in this acetylation-based regulatory mechanism might change the average onset of cancers or neurological diseases to well beyond the current human lifespan."

"Clearly, a simple preventative approach would be a key, not to immortality, but to longer, disease-free lives," added Bambara.

DNA replication is an intricate, error-prone process, which takes place when our cells divide and our DNA is duplicated. Duplicate copies of DNA are first made in separate pieces, that later must be joined to create a new, full strand of DNA. The first half of each separate DNA segment

usually contains the most errors, while mistakes are less likely to appear in the latter half.

For DNA that travels down the standard route, the first 20 percent of each separate DNA segment is tagged, cut off and removed. This empty space is then backfilled with the latter part – which is the more accurate section – of the adjoining piece of DNA as the two segments come together to form a full strand.

In contrast, DNA that travels down the elite route gets special treatment: the first 30 to 40 percent of each separate DNA segment is tagged, removed and backfilled, meaning more mistakes and errors are eliminated before the segments are joined. The end result is a more accurate copy of DNA.

The same situation occurs with the DNA repair process, as the body works to remove damaged pieces of DNA.

Unlike the current work, the majority of aging-related research zeroes in on specific agents that damage our DNA, called reactive oxygen species, and how to reduce them. The new research represents a small piece of the pie, but has the potential to be a very important one.

Bambara's team is investigating the newly identified acetylation regulatory process further to figure out how they might be able to intervene to augment the body's natural safeguarding of important genetic information. They are studying human and yeast cell systems to determine how proteins in cells work together to trigger acetylation, which adds a specific chemical to the proteins involved in DNA replication and repair. Researchers are manipulating cells in various ways, through damage or genetic alterations, to see if these changes activate or influence acetylation in any way.

Though they are far from identifying compounds or existing drugs to test, they do see this research having an impact in the future.

"The translational rate is becoming better and better. Today, the course between initial discovery and drug development is intrinsically faster. I could see having some sort of therapeutic that helps us live longer and healthier lives in 25 years," said Bambara.

Provided by University of Rochester Medical Center