Scientists identify protein that improves DNA repair under stress

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Cells in the human body are constantly being exposed to stress from environmental chemicals or errors in routine cellular processes. While stress can cause damage, it can also provide the stimulus for undoing the damage. New research by a team of scientists at the University of Rochester has unveiled an important new mechanism that allows cells to recognize when they are under stress and prime the DNA repair machinery to respond to the threat of damage. Their findings are published in the current issue of *Science*.

The scientists, led by biologists Vera Gorbunova and Andrei Seluanov, focused on the most dangerous type of DNA damage – double strand breaks. Unrepaired, this type of damage can lead to premature aging and cancer. They studied how oxidative stress affects efficiency of DNA repair. Oxidative stress occurs when the body is unable to neutralize the highly-reactive molecules, which are typically produced during routine cellular activities.

The research team found that human cells undergoing oxidative stress synthesized more of a protein called SIRT6. By increasing SIRT6 levels, cells were able to stimulate their ability to repair double strand breaks. When the cells were treated with a drug that inactivated SIRT6, DNA repair came to a halt, thus confirming the role of SIRT6 in DNA repair. Gorbunova notes that the SIRT6 protein is structurally related to another protein, SIR2, which has been shown to extend lifespan in multiple model organisms.

"SIRT6 also affects DNA repair when there is no oxidative stress," explains Gorbunova. "It's just that the effect is magnified when the cells are challenged with even small amounts of oxidative stress." SIRT6 allows the cells to be economical with their resources, priming the repair enzymes only when there is damage that needs to be repaired. Thus SIRT6 may be a master regulator that coordinates stress and DNA repair activities, according to Gorbunova.

SIRT6 does not act alone to repair DNA. Gorbunova and her group also showed that, in response to stress, SIRT6 acts on a protein called PARP1 to initiate DNA repair. PARP1 is an enzyme that is one of the "first responders" to DNA damage and is involved in several DNA repair machineries. By increasing the levels of SIRT6, the Rochester team found that cells were able to more rapidly direct DNA repair enzymes to sites of damage and hasten the repair of double strand breaks.

The next step for Gorbunova and Seluanov is to identify the chemical activators that increase the activity of SIRT6. Once that discovery is made, Gorbunova said it may be possible to apply the results to therapies that prevent the onset of certain aging-related diseases.

Provided by University of Rochester

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