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New findings regarding DNA damage checkpoint mechanism in oxidative stress

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In current health lore, antioxidants are all the rage, as "everybody knows" that reducing the amount of "reactive oxygen species"—cell-damaging molecules that are byproducts of cellular metabolism—is critical to staying healthy. What everyone doesn't know is that our bodies already have a complex set of processes built into our cells that handle these harmful byproducts of living and repair the damage they cause.

For example, few of us realize that, while our cells' DNA is constantly being damaged by reactive oxygen species (as well as by other forces), there are also complex mechanisms that constantly assess that damage and make repairs to our fragile genetic material at least 10,000 times a day in every cell in our bodies. The vital biochemical processes by which this constant DNA repair takes place are still only partially understood because of their complexity, speed, and the difficulty of studying complex interactions within living cells. Moreover, it remains unknown how cells sense the oxidatively damaged DNA in the first place.

In an article published in the *Proceedings of the National Academy of Sciences* (*PNAS*) a research team from University of North Carolina at Charlotte announced that they had uncovered a previously unknown surveillance mechanism, known as a DNA damage checkpoint, used by cells to monitor oxidatively damaged DNA. The finding, first-authored by UNC Charlotte biology graduate student Jeremy Willis and undergraduate honors student Yogin Patel, was also co-authored by undergraduate honors student Barry L. Lentz and assistant professor of biology Shan Yan.

"DNA damage is the underlying pathology in many major human diseases, including cancers and neurodegenerative disorders such as Alzheimer's and Parkinson's, so arriving at a full understanding of the sophisticated mechanisms that cells usually employ to avoid such disastrous outcomes is important," Yan noted.

Two biochemical pathways, known as ATM-Chk2 and ATR-Chk1, govern the cell's response and repair of double-strand DNA breaks and other types of DNA damage or replication stress respectively. The molecular mechanisms underlying the ATR-Chk1 checkpoint activation include the uncoupling of DNA helicase and polymerase activities and DNA end resection of double-strand breaks.

"The significance of what we have found is that there is a third, previously unknown trigger for ATR-Chk1 checkpoint pathway, and this novel mechanism is discovered in the context of oxidative stress," Yan said.

In particular, Yan's team discovered that under conditions of oxidative stress (in the presence of hydrogen peroxide) a base excision repair protein known as APE2 plays unexpected roles in the checkpoint response: single-strand DNA generation and Chk1 association. The protein was previously known to be involved in the DNA repair of oxidative damage, but not to extent revealed in the study's findings. The distinct role of APE2 in the single-strand DNA generation in 3' to 5' direction is referred to as single-strand break end resection ("SSB end resection") by the authors.

The study involved experiments performed with Xenopus laves (the African clawed frog, a species commonly used as a lab animal) egg extracts – an experimental system that Yan's lab has developed for studying DNA repair and checkpoint mechanisms in a cell-free conditions. Xenopus is useful because it is a vertebrate (and thus quite

similar to humans in cell biology), and its egg cells can be easily produced and manipulated.

Yan is hopeful that this research will open new avenues to pharmacological strategies in drug development for cancer and neurodegenerative diseases.

More information: www.pnas.org/content/early/201 … /1301445110.abstract

Provided by University of North Carolina at Charlotte