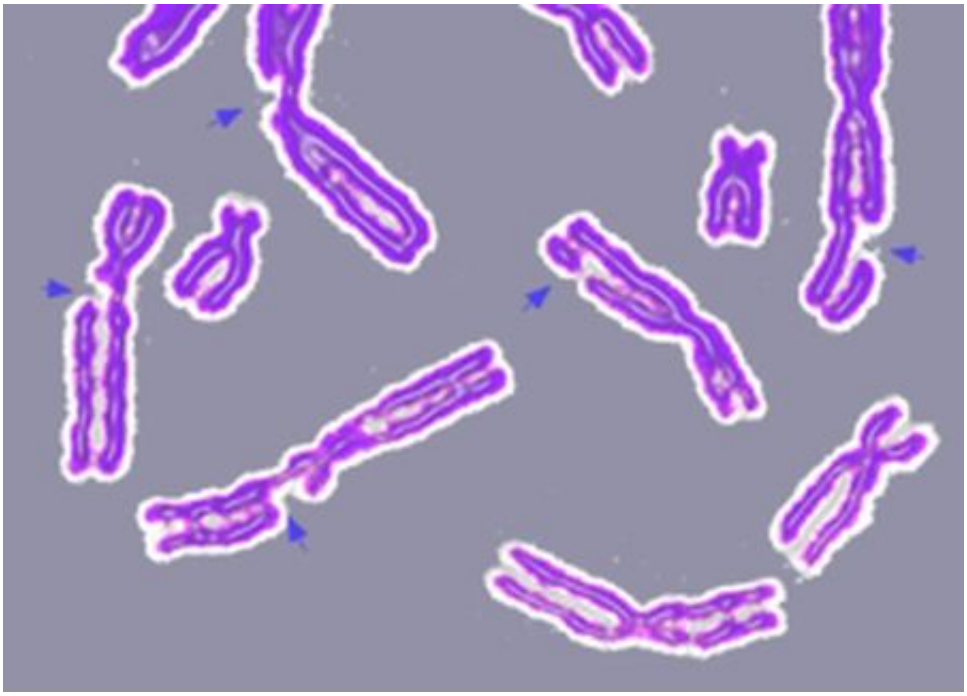
Researchers highlight nucleolar DNA damage response in fight against cancer

March 16 2023



DNA damage resulting in multiple broken chromosomes. Credit: Wikipedia/CC BY-SA 3.0

Cancer, which affects millions every year, requires proteins to spread through the body. In a new strategy to beat the wide-ranging disease, scientists are sabotaging its protein factories.

In a new forum paper published in *Trends in Cell Biology*, researchers from the University of North Carolina at Charlotte encapsulated the

young field of nucleolar DNA damage response (DDR) pathways. The review highlights six mechanisms by which cells repair DNA damage, including one which was published five months ago in *Nucleic Acids Research* by the same authors. By attacking these mechanisms, future applied researchers will be able to trip up cancer's reproduction and growth.

"The whole purpose of the *Trends* paper is to bring attention to scientists in the field and trigger their research," says Shan Yan, the main author. "I did not realize the significance of this field, which is only fifteen years old, until a couple of years ago."

In a groundbreaking 2007 paper published in *Nature*, researchers began the field by unveiling the first pathway within the nucleolus, an area within an organelle, or room, within the cell. Inside the nucleolus, different molecules help copy DNA, which contains the plans for cells. Different factors can cause glitches, such as strand breaks, in the copies. These researchers found a way to help heal glitches when copying ribosomal DNA, or the plans for the protein factories of the cell.

By studying these mechanisms, researchers can target cancer, which relies on ribosomal DNA to make the proteins they need to attack the human body. For instance, a Phase I clinical trial is already underway for a drug that targets the second mechanism listed in the paper—if the cancer cells can't heal glitches, then they can't make new factories and hence can't make new proteins.

While the first four mechanisms take place inside the nucleolus, which is in a room cordoned off within the watery cell, the last two mechanisms use a new cellular process which won the 2023 Breakthrough Prize in Life Sciences. In the process, called liquid-liquid phase transition, proteins pop up their own liquid 'tents' to do their work instead of staying inside a room.

Before working on the nucleolar DDR, Yan researched a protein called APE1. When he discovered that APE1 could locate the nucleolus within a cell and could also pop up these liquid tents to do work, it launched his investigation into these pathways and ultimately to the review paper.

"What's new is that APE1 acts like a GPS or a first responder," Yan said. "It says there's a problem here, we need a police car, a medic, and others to come and be concentrated here."

Basic researchers like Yan will continue to better define these mechanisms, while more applied scientists can then use those mechanisms as points of attack in the war on cancer.

"This is an exciting and emerging area," Yan said. "By testing this idea, and if the clinical trial is successful, then these mechanisms will be tickets into new clinical trials and treatments."

More information: Jia Li et al, Molecular mechanisms of nucleolar DNA damage checkpoint response, *Trends in Cell Biology* (2023). DOI: 10.1016/j.tcb.2023.02.003

Provided by University of North Carolina at Charlotte