Researchers identify promising new target for drug-resistant breast and ovarian cancers

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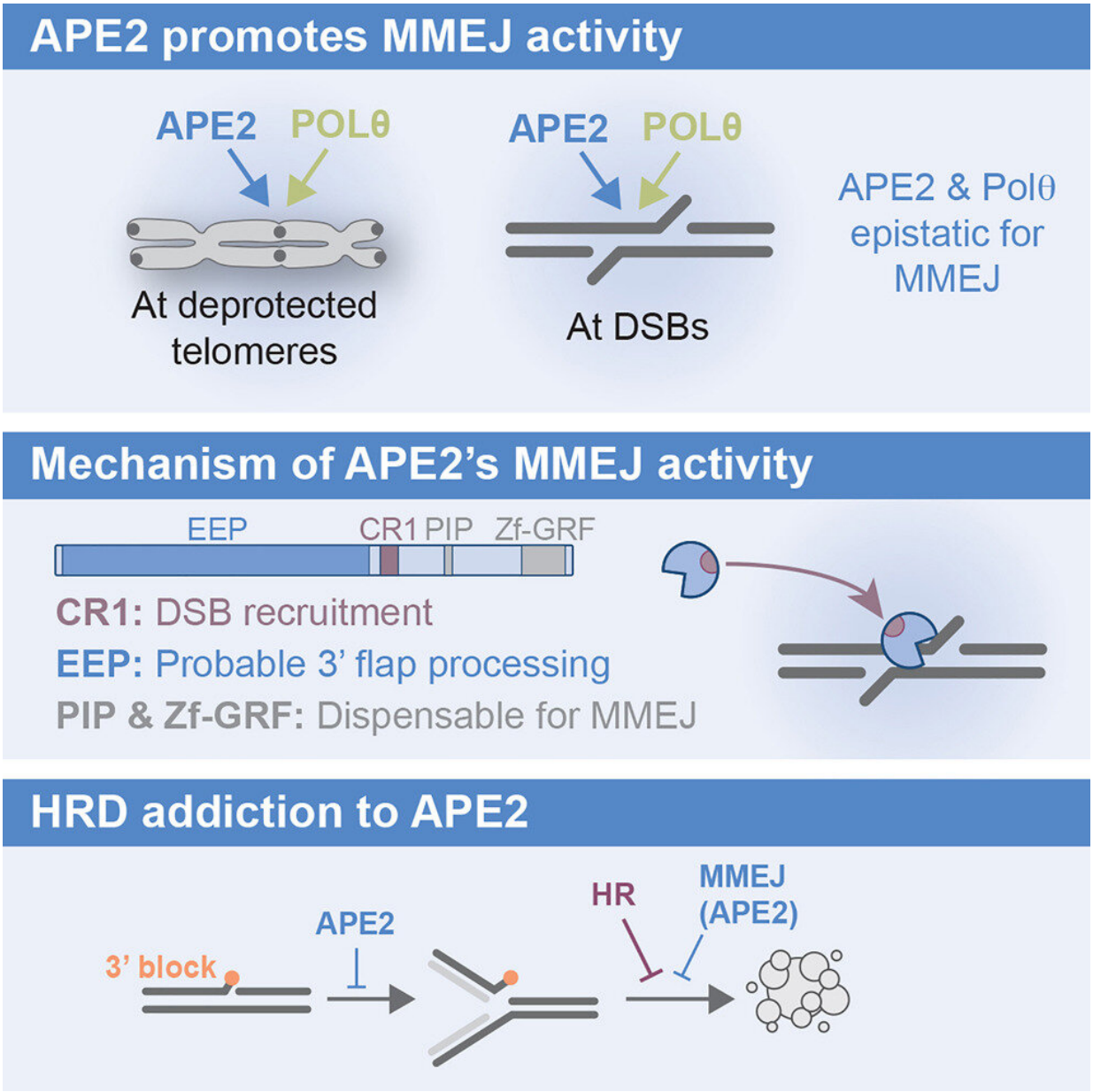

Graphical abstract. Credit: *Molecular Cell* (2023). DOI: 10.1016/j.molcel.2023.03.017

CU Boulder researchers have discovered a protein's crucial role in helping breast and ovarian tumors survive and thrive and have found that suppressing that protein kills cancer cells without harming healthy ones.

The findings, published Tuesday, April 12, in the journal *Molecular Cell*, identify a promising new target for treating cancers fueled by certain genetic mutations, including mutations in the BRCA1 and BRCA2 genes. The research could lead to new therapies that have fewer side effects and work against cancers that have grown resistant to existing treatments.

About 250,000 women are diagnosed with breast cancer each year, and another 20,000 are diagnosed with ovarian cancer annually. As many as 80% of women with the most common type of ovarian cancer become resistant to treatment.

"This is an important breakthrough for all of those women who have resistant cancers and for whom we now have nothing more to offer," said senior author Nausica Arnoult, an assistant professor of molecular, cellular and developmental biology at CU Boulder.

A new approach to fighting cancer

The research centers around what's known as the DNA damage response, a mechanism within all cells that detects damage to the double-stranded helix which carries genetic instructions and takes steps to repair its frayed ends.

"Our DNA constantly gets damaged from the sun, the chemicals we breathe and internal processes, and we and all living organisms have evolved mechanisms to quickly repair that damage," said Arnoult.

When repair mechanisms are faulty, as when people inherit a mutated copy of the BRCA1 or BRCA2 gene, some cells make mistakes and mutations replicate, potentially leading to uncontrolled cell growth or cancer. Mutations can also occur sporadically, due to environmental exposures or other factors.

Ironically, the same faulty repair mechanisms that can lead cancer to form also make cancer cells themselves vulnerable to destruction.

About half of ovarian cancers and a quarter of breast cancers lack a key first-line DNA repair mechanism, called homologous recombination (HR), and must rely on a less reliable pathway known as MMEJ (microhomology-mediated end joining).

In hopes of developing ways to disable that backup pathway, Arnoult and her team set out to better understand it. They observed damaged cancer cells in the lab as they worked to repair themselves and utilized the gene-editing tool CRISPR to isolate which proteins were at play.

They discovered that a protein called APE2 plays an essential role in repairing broken DNA in cancer cells. When they genetically suppressed it, that DNA damage response faltered, and the cancer cells died.

Meanwhile, healthy cells, which could rely on their first-line DNA damage response and didn't need APE2, went unscathed.

"We show that suppression of APE2 selectively kills cancer cells without affecting normal tissues and could be a powerful target to combat breast and ovarian cancers," said Arnoult.

Her team is not the first to go after the DNA damage response—a vulnerability some call cancer's "Achilles heel."

Since 2015, thousands of ovarian and breast cancer patients have been treated with so-called "PARP inhibitors," such as the blockbuster drug olaparib, which works by disabling a different backup DNA self-repair pathway.

Unfortunately, Arnout said, many cancers have grown resistant to such drugs, prompting scientists to search for other pathways and targets.

In future studies, she seeks to identify a small molecule that can inhibit APE2. Such an inhibitor could be given alongside other drugs to improve results or as a second option when resistance occurs.

Arnoult said that many different kinds of cancers have mutations that make them vulnerable to inhibition of other DNA repair factors. By better understanding those distinct pathways, scientists could develop new, targeted therapies for a wide range of resistant cancers.

"We can't put all our eggs in one basket anymore," she said. "For many women, once the cancer becomes resistant, there is no second-line therapy. We need to change that."

More information: Hubert Fleury et al, The APE2 nuclease is essential for DNA double-strand break repair by microhomology-mediated end joining, *Molecular Cell* (2023). DOI: 10.1016/j.molcel.2023.03.017

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