Shedding light on the mechanism of yeast DNA repair

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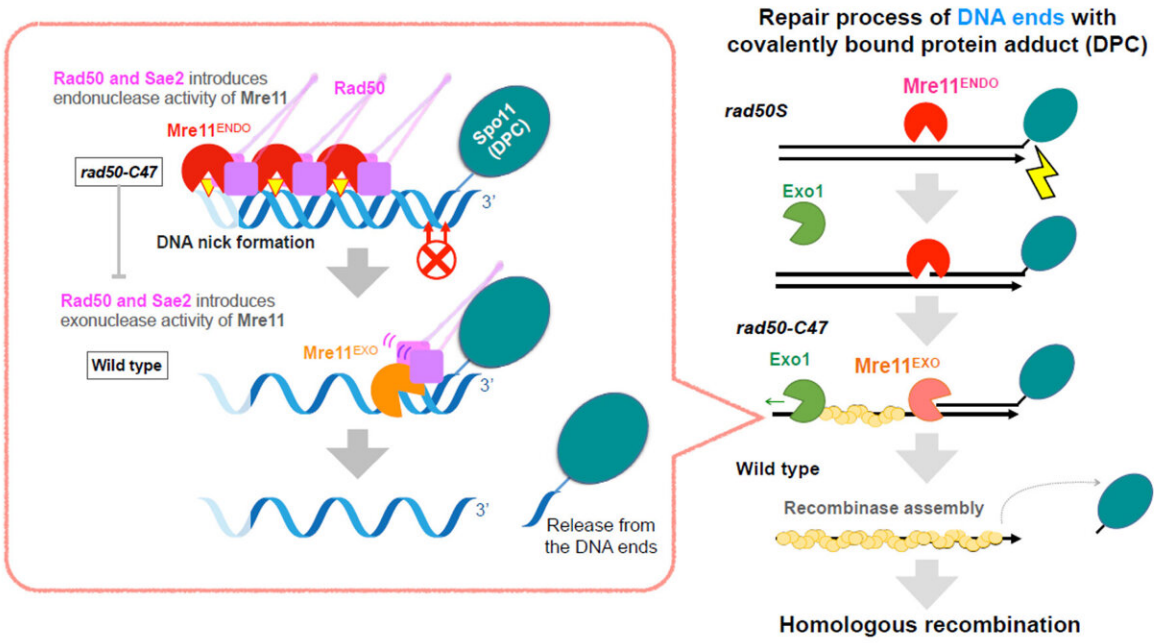

Homologous recombination is a DNA repair mechanism that counteracts double-stranded breaks in DNA. Researchers at Kindai University have recently revealed how the Sae2 protein coordinates with the Mre11-Rad50-Xrs2 complex to activate endonuclease and 3'-5' exonuclease during DNA end resection in budding yeast. Credit: Prof. Miki Shinohara / Kindai University

DNA damage is a cellular phenomenon that introduces structural abnormalities in double-stranded DNA. External factors, such as radiation or chemical agents, as well as internal factors, such as blocked

DNA replication, can generate double-strand breaks (DSBs) in DNA.

To counteract DNA damage, cells engage in DNA repair to preserve genetic integrity and ensure cell survival as failure to repair DSBs has serious health complications like increased risk of cancer.

DSBs are repaired by two mechanisms called non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ is the predominant DNA repair mechanism in human somatic cells and is error-prone. In contrast, HR is active during specific stages of the cell cycle and is error-free.

The Mre11-Rad50-Xrs2 (MRX) trimeric protein complex in yeast is central to HR. Sae2, a cellular protein, coordinates with MRX to stimulate endonuclease and exonuclease activities to initiate DNA end resection. DNA end resection is a two-step process for repairing DSBs.

In the short-range resection, MRX-Sae2 endonuclease introduces a cut in the 5′ strand. It then activates 3'-5' exonuclease to digest a few base pairs from the 5' strand, producing stretches of single-stranded DNA. In the long-range resection, Exo1 exonuclease extends the resection in the 5'-3' direction and helps DNA repair.

In a study published in *Nature Communications* on 22 August 2024, an international research team sought to understand the controlled mechanism and the physiological significance of Sae2 in DNA repair.

The team, comprising Professor Miki Shinohara and Mr. Tomoki Tamai from Kindai University, Japan, Dr. Giordano Reginato and Dr. Petr Cejka from Università della Svizzera italiana, Switzerland, and Dr. Katsunori Sugimoto from the State University of New Jersey, U.S., conducted genetic and biochemical analysis to study how Sae2 controls the two nuclease activities.

Prof. Shinohara explains, "The mechanism by which Sae2 stimulates the MRX endonuclease and 3'-5' exonuclease activities for DNA repair remains unknown. Understanding this mechanism of DNA end processing in DSB repair can enhance our knowledge of the plasticity and robustness of genetic information in organisms."

In a separation-of-function experiment, the researchers identified and introduced the rad50-C47 mutation that affects Sae2-dependent MRX 3'-5' exonuclease activity, but not endonuclease activity.

"Our findings suggest that MRX endo- and exonuclease activities are stimulated by Sae2 via Rad50 through different mechanisms, ensuring coordinated but separate endonucleolytic and exonucleolytic actions of MRX-Sae2 on blocked DNA ends," says Prof. Shinohara.

A detailed understanding of how Sae2 controls Mre11's endo- and exonuclease activities during DNA end resection in DSB repair is crucial for maintaining the robustness of the process that preserves genetic information in organisms.

"Our study reveals the control mechanism for DNA end processing, which is important for suppressing cell tumorigenesis and may provide valuable information for developing novel anti-cancer therapies," concludes Prof. Shinohara.

More information: Tomoki Tamai et al, Sae2 controls Mre11 endo- and exonuclease activities by different mechanisms, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51493-5

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