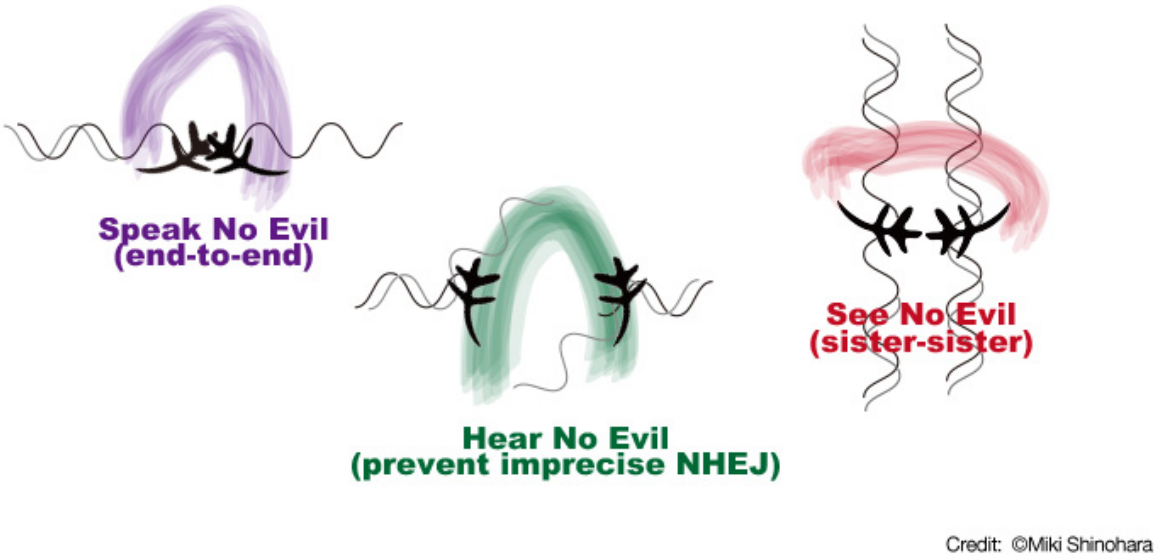
Protein complex prevents genome instability

January 19 2017



Three wise monkeys showing multiple functions of Mre11-Rad50-Xrs2 complex at different types of DNA break. Credit: Osaka University

An international collaboration between Osaka University and the Friedrich Miescher Institute for Biomedical Research (FMI) in Switzerland is investigating the repair process of a serious form of DNA damage that can lead to instability of genetic material and tumor formation. The researchers are studying the roles of groups of proteins that control the repair of double-stranded breaks (DSBs) in DNA that occur from internal or external sources, such as UV irradiation.

The yeast Saccharomyces cerevisiae, also known as baker's or brewer's yeast, is being used by the team as a model organism to study the repair protein functions. This yeast is an ideal model because it shares many similarities with many similarities with plants and animals, all of which are made up of cells with nuclei, yet its genetics are sufficiently simple to allow it to be easily manipulated in the lab. Yeast is therefore an excellent tool to study the different types of genomic mutations that characterize human cancers.

The researchers found that the MRX complex of three yeast proteins plays a vital structural role during early DSB repair and when overcoming delays in the replication of partially separated DNA double helices. "MRX is introduced to the DNA damage site or stalled replication fork through its interaction with yeast replication protein A," says Susan M. Gasser of FMI. "We used super-resolution microscopy to show that this interaction behaves like a linchpin to stabilize broken ends of DNA."

Crucially, their research revealed that this structural role did not require the presence of another protein, cohesin, as was commonly thought.

The Xrs2 member of the MRX complex interacts with other proteins to ensure that the correct molecules are present at repair sites of DNA damage. Strong similarities between regions of yeast proteins and related human proteins are a sure sign that the sequences are functionally important enough not to have changed during evolution. Nbs1, the human equivalent of Xrs2, shares a similar role, and mutations at one end of this protein cause an inherited disease with a high risk of cancer and immunodeficiency.

In a related study, the team found that mutations in the part of Xrs2 equivalent to the disease-causing region of Nbs1 caused the build-up of a protein, Ku, which controls the structure of chromosome ends. "This

reduced the precision of the joining of damaged DNA ends, akin to that seen in the human disease," explains Miki Shinohara of the Osaka University Institute for Protein Research, Department of Integrated Protein Functions. "The same part of Xrs2 was also needed to sustain high activity levels of a key enzyme involved in the DNA damage response."

More information: Andrew Seeber et al. RPA Mediates Recruitment of MRX to Forks and Double-Strand Breaks to Hold Sister Chromatids Together, *Molecular Cell* (2016). DOI: 10.1016/j.molcel.2016.10.032

Daichi Iwasaki et al. The MRX Complex Ensures NHEJ Fidelity through Multiple Pathways Including Xrs2-FHA–Dependent Tel1 Activation, *PLOS Genetics* (2016). DOI: 10.1371/journal.pgen.1005942

Provided by Osaka University