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How cells handle broken chromosomes

Scientists from the Max Planck Institute of Biochemistry discovered a novel cellular response towards persistent DNA damage: After being recognized and initially processed by the cellular machinery, the broken chromosome is extensively scanned for homology and the break itself is later tethered to the nuclear envelope. Thus the researchers uncovered a surprising feature of how DNA strand breaks can be handled. Their unexpected findings have important implications for the understanding of DNA repair mechanisms. (Molecular Cell 33, February 13th, 2009)

The central molecule for life is DNA, which constitutes the genetic blueprint of our organism. However, this precious molecule is constantly threatened by miscellaneous damage sources. DNA damage is a cause of cancer development, degenerative diseases and aging. The most dangerous and lethal type of DNA-damage is the DNA double strand break (DSB). A single DSB is enough to kill a cell or cause chromosomal aberrations leading to cancer. Therefore, cells have evolved elaborate DNA repair systems that are fundamental for human health. DSBs can be repaired by error-prone non-homologous end joining, a pathway in which the DSB ends are simply fused together again. The alternative repair pathway, called homologous recombination, is mostly error-free and needs homologous DNA sequences to guide repair. A vast amount of research, by many scientists around the world, has provided us with a detailed picture of how the DNA damage is recognized and finally repaired. However, so far little was known, how homologous sequences are found and how cells react when DNA breaks persist.

Now, scientists around Stefan Jentsch, head of the Department of Molecular Cell Biology, were able to shed light on these questions, as they report in the upcoming issue of Molecular Cell.

The scientists modified a yeast strain in which a DSB can be induced and followed over time. Moreover, they managed to label the DNA-break for microscopic studies. Using high-resolution



digital imaging, they observed after a few hours a directed movement of the break to the nuclear envelope. Jentsch and colleagues speculate that this tethering to the nuclear envelope could be a safety measure of cells to prevent erroneous and unwanted recombination events, which can have catastrophic consequences like cancer development or cell death.

Marian Kalocsay and Natalie Hiller, who conducted the study as part of their PhD-thesis research, then set out to unravel the molecular details of how a persistent DSB is recognized, processed and – at last - relocated to the nuclear envelope.

Using a high resolution method – the so called chip-on-chip technique - which allowed to investigate repair factor recruitment to DNA in unprecedented details, the researchers made a surprising observation: In an apparent attempt to find homology and repair the DSB, a protein called Rad51 (or “recombinase”) begins within one hour to accumulate and to spread bi-directionally from the break, covering after a short time the entire chromosome – a much larger area than supposed before. “Intriguingly, Rad51 spreading only occurs on the chromosome where the break resides and does not “jump” to other chromosomes”, says Kalocsay. As to the researchers knowledge, this is the first *in vivo* description of ongoing chromosome-wide homology search, which is the most mysterious event in DSB repair. Therefore, this finding has important implications for the understanding of DNA repair by homologous recombination.

Furthermore, Kalocsay and Hiller identified a novel important player in the DNA-damage response that is essential for Rad51 activation as well as for the relocation of DSBs to the nuclear envelope: the histone variant H2A.Z. In early stages of DNA repair it is incorporated into DNA near the DSBs and is essential there for the initiation of the following repair mechanisms. Later on, the attachment of the small modifying protein SUMO to H2A.Z plays an important role in the tethering of the break to the nuclear envelope. “Moreover, cells lacking H2A.Z are severely sensitive to DSBs, thus revealing H2A.Z as an important and novel factor in DSB-repair”, explains Hiller.

Original Publication:

Marian Kalocsay*, Natalie Jasmin Hiller* and Stefan Jentsch: “Chromosome-Wide Rad51 Spreading and SUMO-H2A.Z-Dependent Chromosome Fixation in Response to a Persistent DNA Double-Strand Break”

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