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DNA REPAIR

Time to switch

STOCKBYTE

DNA double-strand breaks (DSBs) are repaired throughout the cell cycle to ensure genome integrity. Non-homologous end joining (NHEJ) and microhomology-mediated end joining (MMEJ) pathways — in which DNA break ends are ligated in the absence of a homologous template — operate in the G1 phase of the cell cycle, but they are prone to errors. An increase in homologous recombination (HR), which is mostly error-free, occurs during the S and G2 phases, even though the NHEJ and MMEJ pathways remain functional. So, how does the cell decide which DSB repair pathway to use and when to switch pathways? Yun and Hiom now identify CTIP (also known as RBBP8) as a molecular switch that directs cells towards HR as they enter S phase.

The authors first observed that cells that lack functional CTIP, which normally promotes HR, are also sensitive to DNA damage in G1 phase. This suggests that CTIP might also function in DNA end joining pathways. Indeed, experiments revealed that CTIP-null cells are defective in DSB repair by both MMEJ and HR, although NHEJ is not compromised. Given that CTIP is phosphorylated on Ser327 as cells enter S phase, CTIP phosphorylation could mediate its role in DSB repair. In fact, CTIP Ser327 phosphorylation is only required for repair by HR, which suggests that this phosphorylation event directs cells away from MMEJ, and towards HR, as they enter S phase. Furthermore, as CTIP Ser327 phosphorylation controls its interaction with BRCA1, which is also necessary for HR, the authors propose that the recruitment of BRCA1 to CTIP could determine the switch from MMEJ to HR as CTIP becomes phosphorylated and cells enter S phase.

> “…CTIP … directs cells towards HR as they enter S phase.”

In short, this study establishes a role for CTIP, and probably BRCA1, in shifting cells from the error-prone repair of DSBs by MMEJ in G1 phase to the accurate repair of DSBs by HR in the S and G2 phases.

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ORIGINAL RESEARCH PAPER Yun, M. H. & Hiom, K. CtIP–BRCA1 modulates the choice of DNA double-strand-break repair pathway throughout the cell cycle. *Nature* 8 Apr 2009 (doi:10.1038/nature07955)

FURTHER READING Branzei, D. & Foiani, M. Regulation of DNA repair throughout the cell cycle. *Nature Rev. Mol. Cell Biol.* **9**, 297–308 (2008)

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