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DNA REPAIR

Working on different ends

When potentially lethal DNA double-strand breaks (DSBs) occur, cells either directly rejoin the DNA ends by non-homologous end-joining (NHEJ), which occurs mainly in the G1 phase, or they repair the DNA by homologous recombination (HR) in the S and G2 phases. But what dictates the type of mechanism that is used? Rodney Rothstein and colleagues found that the chemical nature of the DNA break ends determines the DNA repair pathway.

DSBs are induced by exposing cells to ionizing radiation (IR) that breaks the DNA in several ways and causes 'ragged' DNA-end structures, whereas enzymatic DNA cleavage produces DSBs with chemically defined 'clean' ends (with a terminal 3′- or 5′-hydroxyl group). By monitoring the recruitment of checkpoint and recombination proteins to nuclear foci (the sites of DNA repair) the authors demonstrated that a fraction of the DNA lesions induced by IR in G1 is not repaired by NHEJ but is processed to generate single-stranded (ss) DNA regions that are coated by replication protein A (RPA). These structures persist until S phase, when they are repaired by the HR machinery. Similar experiments showed that, unlike the IR-induced DSBs, endonuclease-induced DSBs are not processed to form RPA-bound ssDNA structures until S phase, so cells must have a way to discriminate between ragged and clean DSBs.

To find out how this is achieved, Rothstein and colleagues monitored the formation of foci in a yeast strain that lacks the DNA-end-binding complex Ku70–Ku80. They found that clean DSBs are processed similarly to ragged DSBs in the G1 phase of mutant cells. Therefore, Ku70–Ku80 protects endonuclease-induced DSBs from being processed to form RPA-bound ssDNA structures and allows the repair machinery to distinguish between the two types of DSB ends.

Cells avoid going through S phase and mitosis with damaged DNA by activating the cell-cycle checkpoint pathway, which keeps cells on hold until DNA repair has occurred. So, do ragged DNA ends activate the cell-cycle checkpoint in G1? The team addressed this question by monitoring the recruitment of cell-cycle checkpoint proteins to IR-induced DSBs in cells that lack the DNA clamp complex 9-1-1. They demonstrated that 9-1-1 alone is responsible for recruiting the cell-cycle checkpoint machinery to damaged DNA in G1. By contrast, when cells enter S phase the 9-1-1 complex and the cyclin-dependent kinase Cdc28 are responsible for this process.

> "...the chemical nature of the DNA break ends determines the DNA repair pathway."

These findings show that not all DSBs are processed equally and that this affects the recruitment of checkpoint and repair proteins to the sites of DNA damage in a cell-cycle-dependent manner.

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ORIGINAL RESEARCH PAPER Barlow, J. H., Lisby, M. & Rothstein, R. Differential regulation of the cellular response to DNA double-strand breaks in G1. *Mol. Cell* **30**, 73–85 (2008)

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