Nature Reviews Molecular Cell Biology | AOP, published online 5 April 2013; doi:10.1038/nrm3564

DNA REPAIR

Repair with a twist

The cellular pathways that preserve genomic integrity, and the proteins involved, have been intensely scrutinized, but a key question is whether results obtained using transformed cell lines and immortalized embryonic stem (ES) cells hold true in primary somatic cells. Here, Jasin and colleagues begin to dissect the homology-directed repair (HDR) cascade in mouse somatic cells and confirm a role for BRCA1 (breast cancer 1), but not ATM (ataxia-telangiectasia mutated) kinase.

The authors generated mice carrying a DR (direct repeat)–GFP reporter, which, upon HDR, expresses GFP. Primary somatic cells from these mice, such as mouse embryonic fibroblasts (MEFs) and ear fibroblasts, showed similar HDR in response to DNA double-stand breaks (DSBs). However, HDR in ES cells was significantly higher (with three to four times as many GFP-positive cells), indicating differences in their repair response.

A key protein in the HDR pathway is BRCA1, which localizes to DSBs and activates downstream homologous recombination components. Consistent with this, MEFs and ear fibroblasts from DR–GFP reporter mice carrying a truncated *Brca1* allele showed significantly reduced levels of HDR compared with wild-type cells. Moreover, the mice were highly sensitive to the DNA cross-linking agent mitomycin C, dying by day 16 after injection. Thus, BRCA1 seems to be necessary for HDR in mouse primary cells.

ATM is also thought to be integral for HDR, acting as an upstream kinase that activates the DNA damage response. Interestingly, the authors found that HDR was not significantly reduced in MEFs and ear fibroblasts from DR–GFP reporter mice carrying an *Atm* truncation mutant or an *Atm* kinase mutant, although DNA damage signalling was defective. By contrast, inhibition of ATM kinase activity in primary ear fibroblasts carrying wild-type ATM markedly decreased HDR.

This finding is consistent with previous work suggesting that loss of ATM and chemical inhibition of its activity have differential effects on HDR. The authors also suggest that it is possible that ATM has a key role in processing other types of lesions. Nonetheless, this study reiterates the importance of assessing how the damage response might vary in different primary cell types.

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ORIGINAL RESEARCH PAPER Kass, E. M. *et al.* Double-strand break repair by homologous recombination in primary mouse somatic cells requires BRCA1 but not the ATM kinase. *Proc. Natl Acad. Sci. USA* 18 Mar 2013 (doi:10.1073/pnas.1216824110)

FURTHER READING Shiloh, Y. & Ziv, Y. The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. *Nature Rev. Mol. Cell Biol.* **14**, 197–210 (2013) | Huen, M. S. Y., Sy, S. M. H. & Chen, J. BRCA1 and its toolbox for the maintenance of genome integrity. *Nature Rev. Mol. Cell Biol.* **11**, 138–148 (2009)

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