Regulation of DNA double-strand breaks repair by chromatin remodelers

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DNA double-strand breaks (DSBs) are highly cytotoxic lesions that must be repaired to ensure genomic stability and avoid cell death. In humans, failure to repair DSBs leads to genomic instability and mutations in genes coding for components of DSB repair systems are linked to cancer and genetic diseases.

DSBs can be repaired by either nonhomologous end joining (NHEJ), or homologous recombination (HR). The key process in determining which pathway is used to repair DSBs is the initial processing of the DSB ends. While NHEJ requires little or no DNA end processing, HR is initiated by nucleolytic degradation of the 5′ terminated strands at both DNA ends by a concerted action of nucleases in a process termed DNA end resection. Following resection, cells can use the sister chromatid as a template for recombination.

In eukaryotic cells, DNA is organized into chromatin, a higher order structure in which it is bound to specific proteins called histones, forming the nucleosomes. The assembly of chromatin reduces the accessibility of DNA which is wrapped up into nucleosomes and then further compacted into chromosomes.

DNA resection occurs in a chromatin context, in which DNA is not directly accessible to the DNA repair factors. For this reason, following a DSB, the surrounding chromatin is modified by specialized factors called chromatin remodelers. Proteins belonging to this category can act in different ways to facilitate the response to DSBs, either depositing post-translational modifications to help the recruitment of DNA repair factors or mechanically moving or eliminating nucleosomes. The latter functions are performed by proteins that can hydrolyze ATP and use the energy obtained to disrupt the interactions between histones and DNA.

Given the conservation of DNA repair pathways, we are using the yeast *Saccharomyces cerevisiae* to investigate the influence of chromatin remodeling on DSBs repair. In particular, we are studying whether deletions and/or mutations in *CHD1*, encoding a monomeric protein involved in assembling, sliding, and spacing of nucleosomes, and *DPB4*, encoding a protein that belongs to both DNA pol epsilon complex and the chromatin accessibility complex Isw2, affect sensitivity to genotoxic agents and DSBs repair.