

P027 Sae2/CtIP-dependent regulation of DNA resection during the cell cycle

Pablo Huertas and Stephen P. Jackson

The Gurdon Institute. University of Cambridge.

DNA double-strand breaks (DSBs) are repaired by two mechanisms: non-homologous end-joining (NHEJ) and homologous recombination (HR). Although HR is the most accurate DSB-repair mechanism, it is restricted to the S and G2 phases of the cell cycle. By contrast, NHEJ operates throughout the cell cycle but assumes most importance in G1. This choice between repair pathways is governed by cyclin-dependent protein kinases (CDKs), with a major site-of-control being at the level of DSB-resection, which takes place most effectively in S/G2. Here, we establish that cell-cycle control of DSB resection in *Saccharomyces cerevisiae* operates via the yeast CDK (Cdc28) phosphorylating an evolutionarily-conserved motif in the Sae2 protein. Thus, we show that mutating Sae2 Ser-267 to a non-phosphorylatable residue causes phenotypes comparable to those of a *sae2* Δ null mutant. Furthermore, a Sae2 mutation that mimics constitutive Ser-267 phosphorylation overcomes the necessity of CDK activity for DSB resection. The above Sae2 mutations also cause cell-cycle-stage specific hypersensitivity to DNA damage, and affect the balance between HR and NHEJ. Finally, we show that this regulation pathway is conserved in human cells, where phosphorylation of CtIP T847 (the homologue residue of yeast Sae2 Ser 267) also controls the CDK dependent activation of DNA DSB resection after several types of damage. These findings therefore provide a mechanistic basis for cell-cycle control of DSB repair and highlight the biological importance of regulating DSB resection.