

S003 Regulation of Rad1/XPF by Slx4 family members

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Budding yeast Slx4 is essential for cell viability in the absence of the Sgs1 helicase and for recovery from DNA damage. Cells lacking Slx4 have difficulties in completing DNA synthesis during recovery from replisome stalling induced by the DNA alkylating agent MMS and this appears to reflect an involvement in error-free bypass of DNA lesions. Slx4 associates physically, in a mutually exclusive manner, with two structure-specific endonucleases – Rad1-Rad10 and Slx1 – but neither of these enzymes is required for Slx4 to promote resistance to MMS. Rad1-Rad10 plays an important role in excision of UV-induced DNA damage but Slx4 is not required for this type of DNA repair. Rad1-Rad10 is also required removal of non-homologous DNA tails during DSB repair by single-strand annealing (SSA) or by homologous recombination and Slx4 is essential for Rad1-Rad10 to carry out these tasks. Phosphorylation of Slx4 by the Mec1 and Tel1 kinases (yeast orthologues, respectively) at a single residue is essential for efficient DNA flap cleavage by Rad1-Rad10. These results indicate that Slx4 has multiple functions in responding to DNA damage and that a subset of these are regulated by Mec1/Tel1-dependent phosphorylation. Recent progress in understanding the mode of action of Slx4 at the molecular level will be discussed and the identification of human SLX4 and its regulation of XPF-ERCC1 will be described.