Supplementary information S4: H. sapiens

**SUPPLEMENTARY INFORMATION**

**Supplementary information S4: H. sapiens**

**S. cerevisiae**

**S. pombe**

Catalytic stimulation
Recruitment/Targeting
Single-Strand Annealing

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Single-Strand Annealing

Catalytic stimulation
Recruitment/Targeting
Single-Strand Annealing

Recruitment of DNMT1

Promotes auto-SUMOylation and SUMOylation of XPF

Functional impact unknown

**NATURE REVIEWS | MOLECULAR CELL BIOLOGY**

In format provided by Dehé & Gaillard (doi:10.1038/nrm.2016.177)
**Structure-specific endonuclease scaffolds.** Schematic representation of structure-specific endonuclease (SSE) scaffolds and summary of how they contribute to SSE regulation. The type of control is indicated below each partner SSE and connected to the pathways that have been shown to rely on this regulation. In addition, for human SLX4 a dotted orange box refers to the recently described SUMO-related functions of SLX4, which rely on its BTB and SIM domains and contribute to SUMOylation of SLX4 itself as well as of XPF\(^1,2\). The SUMO-related functions of SLX4 are not essential for its role in inter-strand crosslink repair but they are needed for the maintenance of the stability of common fragile sites\(^1,2\). During genome wide replication stress the SUMO-related functions of SLX4 amplify genome instability and lead to cell death\(^1\). The functional impact of SUMOylation of SLX4 and XPF has not yet been established. SUMOylation of XPF is reminiscent of the recently reported SUMOylation of Rad1 in *S. cerevisiae*, which reduces its DNA binding properties and has been proposed to be a way to promote recycling of Rad1–Rad10 and help sustain high levels of DNA damage\(^3\). Promiscuity between protein SUMOylation, scaffolds and SSEs is further supported by recent findings on the SUMOylation of Saw1 on K221, which acts as a switch between Saw1–Rad1–Rad10 and Saw1–Slx1–Slx4 complexes\(^3\). Indications in bright pink above the schematic representation of UHRF1 relate to well-established epigenetic control functions of this scaffold\(^{[Fang:2016gy]}\). It is not known whether the recently described interaction between UHRF1 and the MUS81–EME1 and XPF–ERCC1 nucleases\(^4\) can be functionally tied in some circumstances to epigenetic control. Of note, links between SSEs and chromatin modifications might be mediated by functional domains such as the PHD finger of SLX1 nucleases, which could promote recruitment to chromatin regions containing H3K4me3, as described for the PHD finger of RAG2\(^5\). In addition, H3K4me3 peptides where shown to stimulate DNA processing by RAG1–RAG2\(^6\). Whether similar regulatory mechanisms apply to SSEs has not yet been established. Importantly, histone modifications were recently shown to predispose specific genomic regions to breakage\(^7\). Interestingly, whereas Slx4 in *S. pombe* does not interact with Swi10–Rad16, the Pxd1 protein was recently identified as a new scaffold that interacts with Rad16–Swi10 and Dna2–Cdc24\(^{[Zhang:2014cf]}\). It shares some sequence homology with the XPF-binding motif of human SLX4, suggesting that the ancestor Slx4 protein has evolved into a short Slx4 protein that only binds Slx1 and into the Pxd1 protein that binds Rad16–Swi10 and Dna2. Remarkably, Pxd1 stimulates Rad16–Swi10 whereas it inhibits the RPA-mediated activation of the 5’ endonuclease activity of
Dna2[Zhang:2014cf]. This confers important functions of Pxd1 in SSA, mating type switching and removal of Top1-DNA complexes. These antagonistic effects on Rad16–Swi10 and Dna2 endonuclease activities were proposed to promote on one hand the completion of SSA by activating the nuclease activity of Rad16–Swi10, while minimizing genetic-information loss by limiting resection that results from RPA-mediated Dna2 activation.

References: