

RESEARCH ARTICLE

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SUMOylation of yeast Pso2 enhances its translocation and accumulation in the mitochondria and suppresses methyl methanesulfonate-induced mitochondrial DNA damage

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Abstract

Saccharomyces cerevisiae Pso2/SNM1 is essential for DNA interstrand crosslink (ICL) repair; however, its mechanism of action remains incompletely understood. While recent work has revealed that Pso2/Snm1 is dual-localized in the nucleus and mitochondria, it remains unclear whether cell-intrinsic and -extrinsic factors regulate its subcellular localization and function. Herein, we show that Pso2 undergoes ubiquitination and phosphorylation, but not SUMOylation, in unstressed cells. Unexpectedly, we found that methyl methanesulfonate (MMS), rather than ICL-forming agents, induced robust SUMOylation of Pso2 on two conserved residues, K97 and K575, and that SUMOylation markedly increased its abundance in the mitochondria. Reciprocally, SUMOylation had no discernible impact on Pso2 translocation to the nucleus, despite the presence of steady-state levels of SUMOylated Pso2 across the cell cycle. Furthermore, substitution of the invariant residues K97 and K575 by arginine in the Pso2 SUMO consensus motifs severely impaired SUMOylation and abolished its translocation to the mitochondria of MMS-treated wild type cells, but not in unstressed cells. We demonstrate that whilst Siz1 and Siz2 SUMO E3 ligases catalyze Pso2 SUMOylation, the former plays a dominant role. Notably, we found that the phenotypic characteristics of the SUMOylation-defective mutant Pso2^{K97R/K575R} closely mirrored those observed in the *Pso2Δ petite* mutant. Additionally, leveraging next-generation sequencing analysis, we demonstrate that Pso2 mitigates MMS-induced damage to mitochondrial DNA (mtDNA). Viewed together, our work offers previously unknown insights into the link between genotoxic stress-induced SUMOylation of Pso2 and its preferential targeting to the mitochondria, as well as its role in attenuating MMS-induced mtDNA damage.

KEYWORDS

ICL repair, mitochondrial localization, mtDNA repair, Pso2, SUMOylation