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DNA repair mutant *pso2* of *Saccharomyces cerevisiae* is sensitive to intracellular acetaldehyde accumulated by disulfiram-mediated inhibition of acetaldehyde dehydrogenase

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ABSTRACT. Blocking aldehyde dehydrogenase with the drug disulfiram leads to an accumulation of intracellular acetaldehyde, which negatively affects the viability of the yeast *Saccharomyces cerevisiae*. Mutants of the yeast gene *PSO2*, which encodes a protein specific for repair of DNA interstrand cross-links, showed higher sensitivity to disulfiram compared to the wild type. This leads us to suggest that accumulated acetaldehyde induces DNA lesions, including highly deleterious interstrand cross-links. Acetaldehyde induced the expression of a *PSO2-lacZ* reporter construct that is specifically inducible by bi- or poly-functional mutagens, e.g., nitrogen mustard and photo-activated psoralens. Chronic exposure of yeast cells to disulfiram and acute exposure to acetaldehyde induced forward mutagenesis in the yeast *CAN1* gene. Disulfiram-induced mutability of a *pso2*Δ mutant was significantly increased over that of the isogenic wild type; however, this was not found for acetaldehyde-induced mutagenesis. Spontaneous mutability at the *CAN1* locus was elevated in *pso2*Δ, suggesting that growth of glucose-repressed yeast

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produces DNA lesions that, in the absence of Pso2p-mediated crosslink repair, are partially removed by an error-prone DNA repair mechanism. The use of disulfiram in the control of human alcohol abuse increases cellular acetaldehyde pools, which, based on our observations, enhances the risk of mutagenesis and of other genetic damage.

Key words: Acetaldehyde; Interstrand cross-links; DNA repair; Disulfiram; Aldehyde dehydrogenase; Mutation induction

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