

P055 The role of human Snm1A in DNA interstrand cross-link repair.

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DNA interstrand cross-links (ICLs) are a class of extremely cytotoxic DNA lesion, and agents that produce these lesions are commonly used in anticancer therapy. Due to the bifunctional nature of these lesions, the repair of ICLs requires the co-ordination of many repair pathways including nucleotide excision repair, homologous recombination and translesion synthesis. In yeast, the *SNM1/PSO2* gene has been found to be specifically involved in the repair of ICLs. Here we show that human Snm1A (hSnm1A) is able to restore the cross-linking drug resistance of yeast *pso2* disruptants. Both hSnm1A and yeast Pso2 proteins belong to the family of metallo- β -lactamase and exhibit 5'-exonuclease activity. In yeast, *pso2* mutants are epistatic with *RAD3*, but non-epistatic with *RAD52* and *RAD6*. In contrast to other NER mutants, *pso2* mutants showed normal incision of ICLs. This places Pso2 functionality after NER incision but before HR and TLS. Along with its 5'-exonuclease, it is likely that yeast Pso2 or hSnm1A is involved in the processing of unhooked ICL intermediates and is likely to have a role in determining the choice of downstream pathways. To further characterise the role of hSnm1A in ICL repair, we used RNA interference to deplete hSnm1A expression in HeLa cells. This results in sensitisation to interstrand cross-linking agents. Work is currently in progress to further explore the temporal and spatial involvement of hSnm1A in the repair of ICLs.