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Interstrand Crosslink Resistance in Escherichia Coli

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Interstrand Crosslink Resistance in *Escherichia coli*

**Abstract:**

8-methoxypsoralen is a photosensitizing agent that blocks DNA synthesis. When DNA is damaged, it can be repaired or tolerated by cells. Interstrand crosslinking (ICL) agents are potent chemotherapeutics, yet the mechanisms by which cells tolerate ICLs are not well understood. In this study, we characterized how cells survived PUVA treatment in the absence of HscAB, and when these gene products were overexpressed.

**Introduction:**

Interstrand crosslinks inhibit replication and transcription in all cells, leading to severe cellular toxicity. Interstrand crosslinks prevent the physical separation of DNA strands and block replication and transcription. Interstrand crosslinking agents are potent chemotherapeutics, yet cancer cells often develop resistance to these drugs through unknown mechanisms. The model organism *E. coli* encodes genes for most of the cellular processes thought to be involved in resistance to interstrand crosslinks in human cells, including nucleotide and base excision repair and translesion DNA synthesis.

Therefore, we sought to identify genes contributing to ICL-resistance in *E. coli* by using targeted mutagenesis and a general selection scheme.

**Conclusion:**

The absence of HscAB was found to have no measurable effect on cell survival following PUVA treatment. Plasmids containing HscAB were toxic to cells even in the absence of PUVA treatment, such that overexpression of HscAB as a mechanism of ICL resistance could not be tested. A population of ICL hyper-resistant cells was isolated over successive generations that had >10^6 magnitude of cell survival to PUVA treatment compared to its wild-type parent. Sequencing of this hyper-resistant strain will be performed to identify genes contributing to the altered phenotype.

Acknowledgements: This work was funded by the NIH grant, R15ES025953

...even in the absence of PUVA damage and induction of HscAB overexpression, cells containing plasmids with hscAB were less viable.

**Figure:**

Sequential selection and re-exposure of cultures to PUVA treatment led to increased resistance to ICL-inducing agents.

**Image:**

[Image of graphs showing survival rates under different UVA doses for various strains of *E. coli*.]

**Table:**

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<tr>
<th>Parent Strain</th>
<th>Gen 2</th>
<th>Gen 3</th>
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<th>Gen 5</th>
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<th>Gen 7</th>
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<tbody>
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<td><strong>% Survival</strong></td>
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