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Journal club

ICLS: A CHICKEN WITHOUT AN EGG

DNA interstrand crosslinks (ICLs), which arise when chemical bonds are formed between the two DNA strands, can block DNA replication and transcription when left unrepaired, leading to cell death. These toxic effects have long been exploited in the clinic by treating patients with cancer with ICL-inducing agents. Moreover, these effects are evident in patients with Fanconi anaemia, whose inability to repair ICLs leads to devastating consequences, including developmental defects and cancer predisposition. Years of studying this disease have unravelled the Fanconi anaemia pathway, through which healthy cells sense, process and ultimately repair ICLs.

Despite all of our knowledge about ICL repair, a key piece of the puzzle is still missing: what are the endogenous sources of ICLs and thus the reason for the evolution and striking conservation of the Fanconi anaemia pathway? Two recent papers provide the first clues. Langevin *et al.* show that the Fanconi anaemia pathway is crucially required to suppress the toxic effects of alcohol in mice that are unable to process acetaldehyde, which is the catabolite of ethanol. The authors also provide direct links between ethanol exposure, ICL repair and fetal alcohol syndrome: mouse embryos that are genetically deficient for alcohol catabolism and the Fanconi anaemia pathway suffer severe developmental defects when their mothers are exposed to ethanol. But the ramifications of this study could be even greater, as it potentially explains why ethanol consumption is a risk factor for cancer development. The authors also suggest that administration of low doses of ethanol to induce the expression of the enzyme alcohol dehydrogenase could potentially be used to alleviate the symptoms of patients with Fanconi anaemia.

> “formaldehyde … could potentially be the more abundant source of ICLs”

In a follow-up study, Rosado *et al.* consolidate the proposed concept by showing that chicken cells that cannot catabolize formaldehyde depend on the Fanconi anaemia pathway for survival. In contrast to acetaldehyde, formaldehyde is a naturally occuring by-product of intracellular reactions, such as histone demethylation, and thus could potentially be the more abundant source of ICLs under physiological conditions.

Although direct evidence that aldehyde metabolites react with cellular DNA to generate cytotoxic ICLs is still lacking, this work certainly provides the field with a ‘smoking gun’ for further studies.

Simon Bekker-Jensen and Niels Mailand
Ubiquitin Signaling Group,
Novo Nordisk Foundation Center for Protein Research,
University of Copenhagen,
Blegdamsvej 3B,
DK-2200 Copenhagen, Denmark.
e-mail: simon.bekker-jensen@cpr.ku.dk

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ORIGINAL RESEARCH PAPERS Langevin, F. *et al.* Fancd2 counteracts the toxic effects of naturally produced aldehydes in mice. *Nature* **475**, 53–58 (2011) | Rosado, I. V. *et al.* Formaldehyde catabolism is essential in cells deficient for the Fanconi anemia DNA-repair pathway. *Nature Struct. Mol. Biol.* **18**, 1432–1434 (2011)