

## **Ethanol Induction of Colorectal Tumours and Precursors in a Mouse Model of Lynch Syndrome**

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Lynch Syndrome (LS) confers inherited cancer predisposition due to germline mutations in one of the DNA mismatch repair (MMR) genes. MMR is a DNA-damage repair pathway involved in the removal of base mismatches and insertion/deletion loops caused by several endogenous and exogenous factors. Loss of MMR through somatic alteration of the wild-type allele in LS results in defective MMR (dMMR). Ethanol and its metabolite acetaldehyde, are classified as group one carcinogens by the IARC. Aldehydes are very reactive molecules that constitute a serious threat to cellular integrity by causing a range of DNA lesions. However, DNA repair pathways responsible for correcting such lesions remains unknown. We hypothesized that MMR plays a role in protecting the cell from ethanol/acetaldehyde induced DNA damage. In this study, we aim to determine if there is a gene-environment interaction between dMMR and ethanol/acetaldehyde that accelerates colorectal tumourigenesis. We used a conditional Msh2 knockout mouse model that mimics the LS patients' pattern of MMR gene inactivation. The LS model mice (6-8 weeks of age) were fed either with 20% ethanol in drinking water or normal drinking water. Most of the ethanol-treated mice demonstrated large intestinal hyperproliferation, adenoma formation and, in some cases, invasive adenocarcinoma within 6 months (11/15), compared with one case of intestinal tumour formation after 15 months in the water-treated mice (1/15). The quantification of the dMMR crypts in LS mouse colon has shown an increased number of dMMR foci in ethanol-treated mice compared with the control group. Preliminary results indicate that long-term ethanol treatment induced acceleration of dMMR-driven large intestinal tumour formation. Possible mechanisms may include increased DNA damage/mutation rate and selection by avoidance of apoptosis that leads to an acceleration in intestinal tumour development.

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