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Mutational signatures of ethanol and acetaldehyde in experimental models

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1- Introduction

Alcohol use is associated with cancer development at various anatomical sites including oral cavity, and is responsible for ~13% of all cancers worldwide. Despite strong epidemiological evidence, the mechanisms of ethanol carcinogenicity in the oral cavity remain unclear. Ethanol's main metabolite acetaldehyde (AcA) may play a crucial role in head and neck cancers by forming covalent DNA adducts that can be mutagenic and may contribute to cancer development. We hypothesized that the role of AcA in alcohol-related oral cancer is based on the formation of specific mutational signature(s) which can be identified in suitable experimental systems.

2- Methods

Using a multi-system experimental approach, we aimed to characterize the mutagenic modes of action of ethanol and AcA at the genome scale level. Firstly, we analyse oral tumour tissues derived from ethanol- and AcA-driven carcinogenesis studies in longitudinally exposed rats, by using whole genome-sequencing (WGS). The animal study is complemented by in vitro chronic AcA exposure of non-tumour hTERT-immortalized oral cell lines, followed by clonal expansion and WGS. Mutational signatures are identified in the genomes of the rat tumours and exposed cells, and are matched with the pre-mutagenic DNA lesions identified by LC-MS/MS DNA adductomic analysis of the cell exposure models.

3- Preliminary results

Oral squamous cell carcinomas collected from the cheeks of rats exposed to 10% ethanol in drinking water have been sequenced at genome scale. We observed mutation patterns (COSMIC signature SBS17) consistent with a possible role oxidative DNA damage processes linked to inflammation and cell keratinization. In the rat oral tumours analysed thus far, we have not detected the COSMIC signature SBS16 putatively linked to alcohol drinking.

4- Next steps

The in vivo findings are being extended to additional cancer sites, including the zymbal gland and forestomach, where ethanol/AcA exposure-associated tumour formation had been observed. The analysis of AcA exposure impact on the cell line genomes is underway and will be integrated with AcA-induced DNA adductome analyses.
We anticipate that this study will improve our understanding of the mechanisms by which ethanol and AcA induce the cancer formation, to ultimately support cancer prevention measures.

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