



MEETING ABSTRACT

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Disruption of DNA methylation via S-adenosylhomocysteine is a key process in high incidence liver carcinogenesis

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Modifications in histologically normal tissue distal to tumours are increasingly evident and the role of such molecular events in tumour susceptibility or in response to presence of a tumour is unclear. We have exploited the ability to explain distal tissue modifications in the dab fish (*Limanda limanda*) which has an unprecedented high occurrence of hepatic adenoma (up to 20%) when analysed from the natural environment. To investigate this, three tissue categories of hepatocellular adenoma, histologically normal liver tissue distal to tumours and livers of non-tumour-bearing dab were used. A multi-“omics” approach was used to provide a comprehensive understanding of the key molecular abnormalities. A remarkable and consistent global hypomethylation, modification of CpG island methylation, gene expression and disruption of one-carbon metabolism was discovered in normal tissue distal to tumours compared to livers of non-tumour-bearing fish. The mechanism of this disruption is linked, not to depletion of S-adenosylmethionine, as is often a feature of mammalian tumours, but to a decrease in choline and elevated S-adenosylhomocysteine, a potent inhibitor of DNA methyltransferase. This novel feature of normal-appearing tissue of tumour-bearing fish helps to understand the unprecedentedly high incidence of tumours in fish sampled from the field and adds weight to the controversial epigenetic progenitor model of tumourigenesis.

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