CLINICAL EPIGENETICS

MEETING ABSTRACT Open Access

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

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From Birminghm Cancer Epigenetics Conference; Translational Opportunities
Birmingham, UK. 16 May 2013

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 methytransferase. 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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Published: 19 August 2013

doi:10.1186/1868-7083-5-S1-S9
Cite this article as: Mirbahai *et al.*: Disruption of DNA methylation via *S*-adenosylhomocysteine is a key process in high incidence liver carcinogenesis. *Clinical Epigenetics* 2013 **5**(Suppl 1):S9.

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