and BRAF mutations have frequently been observed in serrated polyps. BRAF has been suggested to yield more potential to malignant progression. This study shows that KRAS mutations are equally important in the development of serrated adenocarcinoma.

Sporadic MSI-H cancers have been suggested to evolve via the serrated route. This suggestion has been drawn from the high frequency of MSI-H in serrated adenomas. In the present study MSI-H was observed in both serrated and conventional cancers, but only in serrated cancers it was associated with BRAF mutations.

The 75.7% frequency of KRAS and BRAF mutations in the serrated adenocarcinomas further supports the idea that the oncogenic activation of either of these genes is essential for the development of serrated cancer. As BRAF mutations were completely absent in the conventional cancers, it is likely that sporadic colorectal cancers representing with mutated BRAF originate via the serrated pathway.

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The thyroid hormone receptor b1 act as a potent suppressor of tumor invasiveness and metastasis

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Thyroid hormone receptors (TRs) play multiple roles in normal proliferation and homeostasis, whereas aberrant TR activity results in endocrine and neoplastic diseases. Although TRs are ubiquitously expressed in normal tissues, reduced TR expression, as well as alterations in TR genes, are common events in cancer. In order to study the role of TRb1 in tumorigenesis, invasiveness and metastasis formation, and since altered TRs are found in breast and liver cancer, we re-expressed the TRb1 isoform in breast cancer and hepatocarcinoma human cell lines. Expression of several angiogenic, epithelial and mesenchymal markers was analyzed in tumors formed by breast cancer cells inoculated orthotopically into the fat mammary pad and by hepatocarcinoma cells injected heterotopically into the flanks of nude mice. In order to study the role of TRb1 in metastasis development, cells were injected into the mice tail vein. The invasive capacity of the cells in culture, as well as the expression of genes and the activity of signaling pathways involved in tumor invasiveness and metastasis formation was also examined.

We have observed that expression of TRb1 in hepatocarcinoma and breast cancer cells reduces tumor growth, causes partial mesenchymal to epithelial cell transition and has a striking inhibitory effect on angiogenesis, invasiveness, extravasation and metastasis formation in nude mice. These changes correlate with the reduced ability of TR-expressing cells to grow in the absence of a solid substrate and to migrate through a matrigel matrix. The underlying mechanism for these TRb1 actions appears to be the down-regulation of expression of genes required for tumorigenesis and metastasis formation and the reduced response of signaling pathways, such as MAPK and PI3K. Thus, we have found that TRb1 represses expression of genes that have been clinically correlated with metastasis formation. These genes include among others growth factor and chemokine receptors, metalloproteases, COX2 and ID1. In addition, TRb1 increases the expression of the anti-metastatic genes caspase1 and IGFBP3. Finally, the receptor blocked the proliferative response to growth and transforming growth factors by antagonizing activation of signaling pathways such as MAPK or PI3K.

These results define a novel role for TRb1 as a tumor and metastasis suppressor gene,and provides a starting point for the development of novel therapeutic strategies for the treatment of human cancer.

POSTER SESSION

General, molecular and genetic epidemiology 1

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p53PIN3 polymorphic motif involved in G-quadruplexes: effect on alternatively spliced p53 transcripts

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The tumour suppressor protein p53 is activated by several stresses to regulate proliferation, apoptosis and DNA repair. This protein corresponds to a full-length product, termed TAp53, and is encoded for by the fully spliced p53 mRNA (FSp53). Its suppressor activities are counteracted by a N-terminal truncated isoform, ?Np53, generated by an alternatively spliced mRNA retaining intron 2 (p53I2). In addition, several common polymorphisms are found in the TP53 gene including p53PIN3, a 16bp duplication in intron 3 (A1: non-duplicated allele; A2: duplicated allele), which is associated with an altered cancer risk and a reduced level of p53 mRNA. In this study, we investigated whether the p53PIN3 polymorphism may impact on the levels of p53 transcripts. We demonstrated using a reverse transcriptase elongation assay that G-quadruplex structures overlap the p53PIN3 sequence and that their topologies are dependent upon the p53PIN3 status. In A1 cells, site-directed mutagenesis and treatment with TMPyP4, a cationic porphyrin, which modulates G-quadruplex formation, showed that disruption of the G-quadruplexes favours the retention of intron 2 and thus the production of FSp53 mRNA. In A2 cells, the same experiments showed that G-quadruplexes are also involved in p53 mRNA expression, but that other mechanisms of mRNA processing are involved, suggesting a complex pattern of p53 mRNAs expression depending on p53PIN3 status. Analysis of both FSp53 and p53I2 transcripts in lymphoblastoid cells, carrying either A1 or A2 allele, revealed a large decrease of these two transcripts in A2 cells compared to A1 cells. This reduction may be explained in part by the influence of G-quadruplexes on alternative splicing of p53. The polymorphic nature of the G-quadruplexes provides both a mechanism for the regulation of the alternative splicing of intron 2 leading to Np53 isoform production and for the genetic susceptibility associated with A2 p53PIN3 allele.

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Alcohol drinking and head and neck cancer: a meta-analysis on aldehyde dehydrogenase-2 evidence a causal relationship from mendelian randomisation

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Background. Individuals homozygous for *2 variant allele of the Aldehyde dehydrogenase-2 (ALDH2) gene are unable to metabolize acetaldehyde, that prevent them from alcohol drinking, while 1*2 heterozygotes have 6-fold higher blood acetaldehyde concentration with respect to 1*1 post-alcohol consumption. If acetaldehyde is pathogenetic, 2*2 should be protected from head and neck cancer and 1*2 being at higher risk. Since this polymorphism is distributed randomly during gamete formation, its association with head and neck cancer should be unconfounded by smoking. We carried out a meta-analysis of ALDH2 and head and neck cancer association studies, and we investigated the consistency between the expected odds ratio for head and neck cancer among drinkers from the largest pooled-analysis among never smokers, and the observed odds ratio from our meta-analysis.

Methods. We searched Medline and Embase up to 31st January 2008, for all relevant studies on the association between ALDH2 polymorphism and head and neck cancer. Authors of the eligible papers were invited to provide genotype data stratified for selected covariates. Pooled odds ratio and 95%CI were calculated by random effects model. Consistency between the expected and observed odds ratio was assessed by an interaction test.

Results. Six studies were selected, with a total of 945 cases and 2917 controls. Risk of head and neck cancer was reduced among 2*2 homozygotes [OR of 0.64 (95%CI: 0.39-1.03)] relative to 1*1, and increased among heterozygotes [OR of 1.83 (95%CI: 1.21-2.77)] especially if heavy drinkers. The expected odds ratio for head and neck cancer due to alcohol intake compared with never drinkers based on the pooled-analysis was 1.40 (95%CI: 0.89-2.21) in 1*1 individuals. In our meta-analysis the odds ratio for head and neck cancer was 1.56 (95%CI: 0.97-2.56) among 1*1 homozygotes compared to 2*2 (p-value for interaction = 0.75).

Conclusion. These data support the theory that alcohol raises head and neck cancer risk through the carcinogenic action of acetaldehyde and the concordance between the expected and observed odds ratio is consistent with a causal role of alcohol in head and neck cancer aetiology.