Results show a strong staining of blood vessels with some degree of diffusion into the surrounding stroma of both normal and metastatic tissue. Organs were homogenized and processed as previously described.

A total of 36 samples was analyzed by mass spectrometry resulting in the identification of 9481 different peptides which could be clustered to 1902 proteins. More than 500 proteins were exclusively identified in tumor samples but neither in healthy livers nor in negative controls. The choice of candidate marker proteins, the expression of suitable domains and the selection of monoclonal antibodies by phage display technology is ongoing.

CONCLUSIONS: In this study we show successful chemical modification of membrane proteins of selected mouse models which closely mimic the metastatic spread of colorectal cancer. Our proteomic results allow for the first time the creation of comprehensive tissue specific protein lists which promises to identify novel TAA easily reachable by antibody derivatives for the therapy and diagnosis of metastatic colorectal carcinoma.

06 July 2008 14:35 - 16:05

PRESIDENTIAL SESSION
APPLIED BIOSYSTEMS – EACR 40TH ANNIVERSARY RESEARCH AWARDS

Cancer genetics

38 Oral

Screening 101 renal cancers for somatic mutations in 3,726 genes

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Around 190,000 new cases of renal cancer are diagnosed in the world each year. Despite the frequency of this type of cancer, little is known about the genetic events involved in sporadic renal carcinoma. One notable exception is the VHL gene which has a deleterious somatic mutation in around two thirds of all clear cell renal cancers. A recent screen for somatic mutations in protein kinases failed to identify any genes with substantial evidence for involvement in the disease.

We report here results of sequencing the coding exons of 3,726 genes in a collection of 101 DNA samples from 96 primary cancers and 5 renal cancer cell lines, each with a matched normal DNA sample. The gene set was derived from several sources including gene families where one member has previously been shown to be mutated in human cancer, genes resident in amplified regions of human cancer genomes, and genes found to be targeted in mouse mutagenesis screens for cancer.

Over 300 somatic mutations were uncovered in the course of this screen. Consistent with our previous analysis of protein kinase gene mutations, renal cancer mutation prevalence is towards the lower end of the spectrum when compared with cancers derived from other tissues. The number of mutations found varied significantly between individual cancers. Over 200 genes were found to have at least one somatic mutation and in most cases these genes harboured only one or two somatic mutations. The mutation spectrum in renal cancers was noted to be different to other cancer types in several instances. Deletion mutations, often localised to poly-nucleotide tracts, are almost 5 times more prevalent than observed in other cancer types we previously screened (mainly lung, breast and melanoma cell lines). The prevalence of C:G>T:A type substitutions was approximately 20% lower than observed in these other cancers while T:A>C:G type substitutions were around 10% more prevalent.

The scale of this sequencing project has allowed both the mutation prevalence and mutation spectrum of individual renal tumours to be studied in depth and allowed comparisons between primary tumours and renal cell lines. It was interesting to note that in contrast to other tumour types (e.g. breast or melanoma) mutation prevalence and spectrum in individual renal cancers was relatively homogeneous. One notable exception was an apparent deletion phenotype observed in some primary renal tumours and cell lines. Further investigation of somatically mutated genes identified in this screen will likely provide insights into renal cancer development.

39 Oral

The impact of defined Brca1 mutations on tumor development, drug response and acquired resistance

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Women with heterozygous germline mutations in BRCA1 have a strongly increased lifetime risk of developing breast and/or ovarian cancer. To study the role of BRCA1 and in breast tumorigenesis, we have developed a conditional mouse model (K14cre;Brca1$^{F/F}$;p53$^{F/F}$) for BRCA1-associated breast cancer. Intervention studies in this mouse model have shown that BRCA1-deficient tumors are more sensitive to platinum drugs than to other conventional chemotherapeutic agents. Strikingly, the Brca1$^{D/D}$;p53$^{D/D}$ mouse mammary tumors (which lack Brca1 exons 5-13) do not become resistant against platinum drugs, suggesting that (partial) BRCA1 function is required for platinum resistance. We therefore hypothesize that genetic reversion of BRCA1 alleles with truncation mutations may underlie the induction of platinum resistance. In line with this notion, preliminary clinical data suggest that in BRCA1 mutation carriers with advanced ovarian cancer (who receive systemic therapy with carboplatin) the survival time is also affected by the type of founder mutation, since the BRCA1^{5382insC} founder mutation appears to be associated with a relatively favorable survival time, compared to the BRCA1^{185delAG} mutation. To investigate whether different founder mutations are indeed causally related to differences in sensitivity to platinum-based chemotherapy, in vitro cytotoxicity studies and in vivo intervention studies with platinum drugs will be performed, using cell lines and mice carrying these specific BRCA1 mutations. In case resistance to platinum drugs is observed, it will be investigated whether resistance occurs via genetic reversion of BRCA1 and/or via other mechanisms.

Platinum resistance is a serious problem in the treatment of BRCA-related cancers. This research could reveal differences in sensitivity to platinum drugs of different BRCA1 mutations. This insight could lead to various treatment strategies for carriers of different BRCA mutations and thereby hopefully to a better survival.

40 Oral

A genome-wide association study of tag SNPs identify five novel colorectal cancer susceptibility loci

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It has been estimated that genes of low-penetrance are involved in more than a third of all colorectal cancers (CRCs). To identify novel CRC susceptibility loci, we carried out a multi-stage genome-wide association study using two large British case-control cohorts. To maximise the power of our investigation, we decided to enrich the discovery phase (Phase 1) with cases that had a strong family history of colorectal neoplasms and with "hypernormal" cancer-free controls. In Phase 1, we genotyped 550,163 tagging SNPs in 940 cases and 965 controls. Three SNPs approaching genome-wide significance after Phase 1 (rs6983267, rs4939827 and rs4779584) were examined in three replication sample sets comprising 7,473 cases and 5, 984 controls. Across the four sample sets, the associations between these three SNPs remained statistically significant, confirming the existence of susceptibility loci at 8q24.21, 15q13.3 and 18q21.1. To identify additional susceptibility loci, about 40,000 SNPs showing association at P<10-2 in Phase 1 were examined in a second phase using 2,873 sporadic CRC cases and 2,871 population controls. 11 SNPs retaining association at P<10-4 were examined in a third phase of the study that comprised 4,287 cases and 3,743 controls. After this latter phase, two SNPs were taken forward for validation in the four and last phase of our investigation. In Phase 4, we examined 10,731 CRC cases and 10,961 controls from 8 centres from Europe and Australia. In addition to the three previously identified susceptibility loci, we identified two novel associations at 10p14 and 823.3. These five novel susceptibility loci tag potentially interesting candidates that include POU5F1P1, SMAD7 and EIF3S3. Our investigation demonstrated the existence of common susceptibility alleles in CRC predisposition.

41 Oral

Genetic variants of miRNA sequences and non small cell lung cancer survival

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Background: Recent evidence indicates that small, non-coding RNA molecules, called microRNAs (miRNAs), function as tumor suppressors or oncogenes. Mutations, mis-expression or altered mature miRNA processing are implicated in carcinogenesis and clinical behavior.

Materials and methods: We conducted a systematical survey of common SNPs in miRNAs and their surrounding regions and evaluated the associations of four SNPs in pre-miRNAs with non small cell lung cancer (NSCLC) survival.

Results: We found that rs11614913 in hsa-mir-196a-2 was significantly associated with NSCLC survival in the recessive genetic model. Stepwise