182 Poster

CIP2A (Cancerous Inhibitor of Protein Phosphatase 2A) promotes gastric carcinogenesis

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Cancerous Inhibitor of Protein Phosphatase 2A (CIP2A) is a recently identified human oncoprotein that promotes malignant cell growth and cellular transformation (Junttila et al, 130, Cell 2007). However, the clinical role of CIP2A in human malignancies has not been studied as yet.

Results of this study provide first evidence that CIP2A is a prognostic factor in human malignancies. We show that CIP2A immunopositivity associates with poor prognosis in certain subgroups of gastric cancer patients. Depletion of CIP2A in gastric carcinoma cells (AGS, MKN-28, and KATO-III) inhibits their proliferation. CIP2A also promotes c-Myc stability in gastric cancer cells, and these cells are dependent on c-Myc for their proliferation. Importantly, depletion of c-Myc inhibits CIP2A expression levels (protein and mRNA) and c-Myc activation results in increased CIP2A mRNA expression levels.

Taken together these results reveal for the first time the clinical role of CIP2A in a human malignancy. Moreover our results describe a novel positive feedback mechanism between CIP2A and c-Myc.

Altogether; our results indicate that inhibition of CIP2A could be a viable therapeutic approach in gastric cancer patients with CIP2A positive tumours.

183 Poster

FGF9 mutations in colorectal and endometrial cancers

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Fibroblast growth factor 9 (FGF9), initially identified as a glia activating factor, has diverse effects in development and carcinogenesis. It maps to 13q11-12 which is a common area of loss of heterozygosity (LOH) in colorectal carcinomas. Here, we report 10 FGF9 mutations out of 203 colorectal and endometrial tumors and cell lines. One of these mutations (c.563delT) was detected in five different carcinomas (four colorectal and one endometrial). It causes a frameshift and creates a premature stop codon that deletes the last 4 amino acids ($FGF9^{\Delta 205\text{-}208}$). The other mutations included four missense and one nonsense. Analysis of the crystal structure of the mutant proteins predicted that all mutations should lead to loss-of-function. Further analysis of the biological activity of three of these mutations (p.V192M, p.D203G and $FGF9^{\Delta 205\text{-}208}$) showed that the mutant proteins have impaired ability to activate MAPKs cascade in cultured cells expressing FGF receptors. Consistent with the predicted loss-of-function, we observed LOH in 7/9 FGF9 mutant tumors. To our knowledge, this is the first report of somatic FGF9 mutations in human cancers. Further studies will clarify the extent and significance of these mutations in carcinogenesis.

184 Poster

Mouse mammary tumour virus like-virus (MMTV-LV) is present in human prostate, ovarian and endometrial cancers but not lung cancer

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Background Mouse mammary tumor virus (MMTV) is a hormonally regulated, oncogenic virus, responsible for 95% of breast cancer in mice. Several groups have detected human MMTV-like virus (MMTV-LV) envelope (env) gene sequences with 95% homology to MMTV in approximately 40% of human breast cancers. We hypothesized that local hormonal effects might be of primary importance in determining the presence of MMTV-LV in human cancers and have investigated the prevalence of MMTV-LV in human prostate, ovarian, endometrial and lung cancers.

Materials and Methods The prevalence of MMTV-LV env DNA was detemined using nested PCR in 147 prostate, 75 ovarian, 30 endometrial and 30 lung cancers. The MMTV-LV long terminal repeat (LTR) region sequence from 14 prostate cancers and 14 ovarian cancers was compared to 6 published MMTV-like viral sequences from human breast cancer to study sequence variation.

Results MMTV-LV env DNA was detected in prostate cancers (59/147), ovarian cancers (15/75), and endometrial cancers (4/30) but not in lung cancers (0/30), suggesting a dependence of MMTV-LV on hormonally influenced tissues. There was no statistical difference in the rate of MMTV-LV env prevalence previously observed in breast cancers (107/346) to that observed in prostate, ovarian and endometrial cancers. Phylogenetic analysis of the MMTV-LV LTR sequence showed no clustering of the isolates according to tissue type, suggesting that MMTV-LV isolated from different tissues was the same virus with a varied tropism.

Conclusions Unlike the mouse model, MMTV-LV env sequences were detected in human cancers other than breast cancer. This indicates MMTV-LV expression is not breast cancer-specific and may relate to hormone-influenced viral expression, rather than an aetiological role. The co-localization of MMTV-LV with hormone receptors will provide further support for this association.

185 Poster

hCCR4/CNOT complex targets DNA damage signalling pathway after genotoxic stress

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Cancer is one of the leading causes of mortality in developed countries. Platinum-based drugs are among the most active anti-cancer agents, and have been widely used in the treatment of a variety of human tumours. Apart from toxicity, resistance to chemotherapy limits the effectiveness of cancer treatments. Some patients do not respond to chemotherapy treatments and others relapse after a short period of response. Cisplatin, as with other anticancer agents, induces the DNA damage response and also activates a stress signalling pathway. An improved knowledge of the mechanisms underlying the resistance to treatment would generate new therapeutic strategies. The DNA-damage response network is highly complex and involves a multitude of proteins that sense the damage, transduce signals into cells and execute cellular responses. We have done a functional approach, based on Genetic suppressor elements (GSEs) strategy, in order to find new genes involved in cisplatin sensitivity. GSEs are short, biologically active, cDNA fragments that interfere with the function of their cognate gene. Using cisplatin as a selection marker, we identified the hCCR4 /CNOT6 gene that mediates cellular sensitivity to the drug. The precise role of the Ccr4-Not complex has not been determined, but seems to serve as a platform that regulates several different cellular functions in response to changes in environmental signals. Recently, CCR4 was described as playing a role in resistance to ionizing radiation and DNA damage, or replication stress induced by chemicals, in yeast Expression of hCCR4/GSE reduces hCCR4 protein levels in cells. However, mRNA levels are not affected, and this indicates that it could be affecting the protein function. The absence of CCR4 impacts on the sensitivity of mammalian and yeast cells to DNA-damaging agents. Our data indicate that hCCR4 plays a role in the control of cell cycle checkpoint following genotoxic stress; overexpression of hCCR4 appears to target Chk2 phosphorylation. Consequently, cells enter mitosis despite bearing DNA-damaged lesions; a higher proportion of phosphorylated H2A-X is detected in cells expressing hCCR4 when compared to WT controls. This finding introduces a new pharmacological target in the treatment of solid tumours.Our results point to a new protein involved in response-to-therapy and, as such, a new pharmacological target for chemotherapy.

186 Poster

The EBV-encoded EBNA1 up-regulates macrophage migration inhibitory factor (MIF) and induces ERK signalling and the activation of Elk1 in B cell lymphoma

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Backround: The Epstein-Barr virus (EBV) is implicated in the pathogenesis of several germinal centre derived B cell malignancies including Hodgkin's lymphoma (HL) and Burkitt's lymphoma (BL). EBNA1 is an EBV protein that