PO-108 FKBP10 IS AN ONCOFETAL PROTEIN THAT SUPPORTS LUNG CANCER GROWTH BY PROMOTING PROTEIN TRANSLATION ELONGATION

R Maciel Israe*. University of Geneva, Physiology and Metabolism, Geneva, Switzerland

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Introduction Cancer therapy is limited by lack of specificity. Thus, identifying molecules that are relevant for tumorigenesis and selectively expressed by cancer cells is of paramount medical importance. Here, following computational and immunohistological analyses, we found in both mouse and human that FKBP10 is an oncofetal protein that during adulthood is selectively expressed in lung cancer cells. Our results from in vitro and in vivo functional assays demonstrated that FKBP10 downregulation hinders growth of lung cancer cells and tumours owing to decreased cell proliferation. By performing proteomic analysis, we identified several members involved in protein translation as putative FKBP10 binding partners. Ribosomal profiling results indicated that FKBP10 downregulation reduces formation of ribosomal polysomes while translation initiation remains unaffected. Thus, we uncovered FKBP10 as a specific requirement of lung tumorigenesis with a role in protein translation elongation that can be exploited for therapeutic gain.

Material and methods 2 mouse model Immunoblotting and immunoprecipitation, shRNAs, Virus production and transduction; Measurement of 35S-labelled methionine incorporation in cells; Ribosomal profiling; CT-scan imaging.

Results and discussions In this study, we found that FKBP10 is specifically expressed in lung tumours in mice and humans while not expressed in healthy tissues. Importantly, our data show that FKBP10 depletion hinders cancer proliferation both in vitro in human lung cancer-derived cells and in vivo in two lung cancer mouse model. The relevance of this finding is bolstered by an association analysis indicating that FKBP10 expression negatively correlates with survival of patients with lung adenocarcinoma. Here, we found that FKBP10 is present at translating ribosomes and sustains protein translation elongation and protein synthesis in lung cancer cells bearing oncogenic KRAS mutation. Importantly, FKBP10 depletion hinders proliferation of cancer cells. Thus, our results support the notion that FKBP10 is an adaptive mechanism required for the increased protein synthesis demand in proliferating lung cancer cells.

Conclusion In summary, we uncovered FKBP10 as an oncofetal protein specifically expressed in KRAS-driven lung tumours. Depletion of FKBP10 hinders tumour proliferation by a mechanism involving suppression of protein translation elongation. Finally, we propose that inhibition of FKBP10 could be exploited for therapeutic purposes against lung cancer and perhaps other types of malignancies.

PO-109 INTEGRAL MEMBRANE PROTEIN 2A EXPRESSION LEADS TO ENHANCED ANTI-CANCER EFFECTS AND CHEMOSENSITIVITY IN EPITHELIAL OVARIAN CANCER

1SY Kim*, 2SH Cha, 3HJ Lee. CHUNGBUK NATIONAL UNIVERSITY, Department of medicine, Cheongu, South Korea; 4ebiogen Research Institute, Department of Technical research, Seoul, South Korea

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Introduction Integral membrane protein 2A (ITM2A) is a type 2 transmembrane protein. Expression of ITM2A was reported to be regulated by PAX-3, a transcription factor important for muscle, neural, and facial development in vertebrates. However, the biological mechanism of ITM2A is so far unknown.

Material and methods The ITM2A protein expression was down-regulated in epithelial ovarian cancer tissue samples and cancer cells as compared to normal cells (p<0.0001) using immunohistochemistry. Our study was to investigate its anti-cancer effects in ovarian cancer cells and to measure the function of ITM2A by cell proliferation, colony formation, flow cytometry and western blot analysis.

Results and discussions Over-expressing ITM2A in ovarian cancer cells inhibited cell growth through the G2/M cell cycle arrest. A matrigel invasion assay showed that ITM2A-transported ovarian cancer cells reduced the colony formation and attenuated invasiveness of ovarian cancer cells. To assess the chemosensitivity of ITM2A, chemosensitizing effects of ovarian cancer cells were measured using paclitaxel or carboplatin. ITM2A was remarkably reduced the proliferative activities after chemotherapeutic agent treatments. Moreover, ITM2A upregulation in ovarian cancer cells increased protein expressions of PARP, cleaved caspase-3 and p53 after carboplatin treatment.

Conclusion Taken together, our results showed that up-regulation of ITM2A could contribute to poor maintenance of epithelial ovarian cancer, affecting both cell growth and invasion. Furthermore, ITM2A expression leads to increase chemosensitivity to chemotherapy, and has therapeutic potential for ovarian cancer.

PO-110 AKT EXPRESSION IS ASSOCIATED WITH POOR CLINICAL OUTCOME IN OVARIAN CANCER

1M Alabdullah*, 2P Moseley, 3S Madhusudan, 4S Chan, 5E Rakha. 1Academic unit of clinical oncology- city hospital campus -Nottingham university hospitals NHS trust- Nottingham- UK; 2Academic Oncology, Nottingham, UK; 3Academic Oncology Unit, Oncology, Nottingham, UK; 4Academic Oncology Unit, Clinical oncology, Nottingham, UK; 5Academic Oncology Unit, Histopathology, Nottingham, UK

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Introduction Ovarian cancer (OC) is the third most common gynaecological cancer among women worldwide and it is associated with the highest mortality rate among gynaecologic malignancies. There is an urgent need to refine classification of ovarian cancer and identify novel targets. The PI3K/AKT/ mTOR pathway is an intracellular signalling pathway important in regulating the cell cycle. Therefore, it is directly related to cellular quiescence, proliferation and cancer. We aimed to investigate the prognostic role of AKT in ovarian cancer.

Material and methods Investigation of the expression of AKT in ovarian epithelial cancer was carried out on tissue microarrays of 525 consecutive ovarian epithelial cancer cases treated at Nottingham University Hospitals (NUH) between 1997 and 2010 and their expression was correlated to clinicopathological outcomes as well as to recurrence free survival (RFS).

Results and discussions High cytoplasmic AKT expression was significantly associated with serous type of tumour (p=0.042). Furthermore, High AKT protein expression was correlated with poor outcome in terms of Recurrence Free Survival (RFS) (p=0.034). Moreover, by selecting only stage one disease positive AKT expression showed significantly higher chance of worse RFS.
Conclusion AKT protein is a prospectively valuable recurrence predictive biomarker of epithelial ovarian cancer.

PO-111  CAPICUA SUPPRESSES HEPATOCELLULAR CARCINOMA PROGRESSION BY CONTROLLING ETV4-MMP1 AXIS

E Kim*. POSTECH, Life sciences, Pohang, South Korea
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Introduction Hepatocellular carcinoma (HCC) is developed by multiple steps accompanying progressive alterations of gene expression, which leads to increased cell proliferation and malignancy. Although environmental factors and intracellular signalling pathways that are critical for HCC progression have been identified, gene expression changes and the related genetic factors contributing to HCC pathogenesis are still insufficiently understood. In this study, we identify a transcriptional repressor Capicua/CIC as a suppressor of HCC progression and a potential therapeutic target.

Material and methods We used human HCC patients samples, tissue microarray, and TCGA database to check CIC levels between normal and HCC patients. We used various HCC cell lines to check cell proliferation, migration, and invasion activity by using CIC knockdown, CIC overexpression, or ETV4 knockdown cells and so on. Also we used two different mouse models, Xenograft and liver specific CIC knockout mice to evaluate tumour progression, metastasis, or survival.

Results and discussions Expression of CIC is posttranscriptionally reduced in HCC cells. CIC levels are correlated with survival rates in patients with HCC. CIC overexpression suppresses HCC cell proliferation and invasion, whereas loss of CIC exerts opposite effects in vivo as well as in vitro. Levels of polyoma enhancer activator 3 (PEA3) group genes, the best-known CIC target genes, are correlated with lethality in patients with HCC. Among the PEA3 group genes, ETS translocation variant 4 (ETV4) is the most significantly up-regulated in CIC-deficient HCC cells, consequently promoting HCC progression. Furthermore, it induces expression of matrix metalloproteinase 1 (MMP1), the MMP gene highly relevant to HCC progression, in HCC cells; and knockdown of MMP1 completely blocks the CIC deficiency-induced HCC cell proliferation and invasion.

Conclusion Our study demonstrates that the CIC–ETV4–MMP1 axis is a novel regulatory module controlling HCC progression.

PO-112  THE ROLE OF TRANSCRIBED ULTRACONSERVED REGIONS UC160 AND UC346 IN COLORECTAL CANCER PROGRESSION

1A Kottorou*, 1C Sirinian, 2F Dimitrakopoulos, 1A Antonacopoulou, 3H Kalofonos. 1University of Patras, Molecular Oncology Laboratory- Medical School, Patras, Greece; 2University Hospital of Patras, Division of Oncology, Patras, Greece
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Introduction Expression of Transcribed Ultra Conserved Regions (Transcribed Ultra Conserved Regions, T-UCRs) is often deregulated in many types of cancer, including colorectal cancer (CRC). Our previous results showed that T-UCRs Uc160 and Uc346 are methylated in CRC. Additionally, their tumour methylation is associated with time to disease progression (TTP) and appears to be a promising biomarker for CRC. However, their role in CRC progression has not been elucidated to date.

Material and methods Aim of the study was to investigate the role of Uc160 and Uc346 in proliferation, motility and migration in colon cancer cells. For that purpose, Uc160 and Uc346 were cloned into plasmids and three colon cancer cell lines (HT-29, Caco-2 and DLD-1) were transiently transfected. After overexpression of Uc160 and Uc346, proliferation (MTT assay), motility (scratch wound healing assay) and migration (transwell migration assay) rates were evaluated.

Results and discussions Proliferation rates, 48 hour after overexpression, were higher in the transfected cells in all cell lines, compared with the control cells (mock transfected). The most significant differences in proliferation rates were noticed for Uc160 overexpression in Caco-2 (p=0.008) and Uc346 overexpression in DLD-1 cells (p=0.033). Similar results were observed in motility assay, with cells overexpressing Uc160 or Uc346 having higher motility rates compared to control cells in all cell lines. More specifically, most significant differences in motility rates were observed in HT-29 and DLD-1 cells overexpressing Uc160 or Uc346 (p=0.017, p=0.041 and p=0.023, p=0.004 respectively). Further analysis of DLD-1 cells migration confirmed the above results, with higher number of Uc160 or Uc346 overexpressing cells migrating compared to the control cells (p=0.005 for both T-UCRs).

Conclusion T-UCRs Uc160 and Uc346 appear to affect the proliferation, motility and migration rates of colon cancer cells, implicating a complex role in CRC progression.

PO-113  INVESTIGATION OF THE ROLE OF IRF4 IN MELANOMA CELLS

T Emre*, U Sobhiafshar, N Yıldız, B Tufan, E Yılmaz, M Ayhan, E Erkan, C Yenide. Boğaziçi University, Dept. of Molecular Biology and Genetics, Istanbul, Turkey
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Introduction While much progress has been made in melanoma treatment in the recent years, melanoma still remains a generally lethal disease at the metastatic stage. Therefore, discovery of additional critical target genes and pathways, and the development of novel therapeutic approaches remain a priority. Like most cancers, abnormal gene regulatory and epigenetic mechanisms are also linked to melanomas.

The transcription factor interferon regulatory factor 4 (IRF4) was discovered as a factor implicated in immunoglobulin expression in B-cells, and was later shown to perform central roles in immune cell development and function. We have previously demonstrated the critical role of IRF4 in a variety of B-cell cancer cells, and identified its mechanisms of action. These and related work suggested IRF4 pathways as therapy targets in cancer. Several studies implicate IRF4 expression and function also in non-immune cells, such as melanocytes. For instance, a number of genome-wide genetic studies associated variation at the IRF4 gene with pigmentation phenotypes and skin cancers. However, despite the observed genetic links and generally high expression, the role of IRF4 in melanoma remains under-studied and poorly understood.

Material and methods We set out to identify the functions of IRF4 in melanoma cells using genome-wide and cell and molecular biological approaches. We have taken a candidate