**PO-150**

**MODULATION OF THE EXPRESSION OF CASEIN KINASE I ISOFORM ALPHA IN THE INITIATION AND PROGRESSION OF PROSTATE CANCER**

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**Introduction** Prostate cancer (PC) is the first cause of fatality related to the reproductive system in men. One out of seven men encounter this pathology once in their lifetime. Prostate Specific Antigen along with digital rectal exam are the first line of screening for prostate pathologies but numerous studies showed that these techniques lack specificity and in sometimes validity for screening. From this notion comes the need to find new biomarkers and molecular players that help get an early detection and effective treatment of PC. Casein Kinase 1 Alpha (CSNK1A1) is an enzyme involved in multiple cellular processes such as the regulation of the oncogenic Wnt/beta-catenin signalling pathway. Its implication in carcinogenesis and cancer progression is still unclear. In this study, we aim to establish a CSNK1A1 expression profile in BPH and in differently advanced PC grades and to investigate the localization of the enzyme compared to beta catenin in the different samples.

**Material and methods** Formalin-fixed paraffin-embedded human prostatic tissues were collected as follows: 85 BPH, 64 PC and 3 controls. Gene expression was assessed by quantitative RT-PCR of cellular transcripts. Protein localization was monitored by tissue immunostaining for CSNK1A1 and Beta-Catenin. Further in-vitro validation of the results is to be made on normal prostate epithelial cell line and PC cell lines using RT-PCR and western blotting.

**Results and discussions** We were able to identify a continuous increase in the CSNK1A1 expression between controls, BPH and PC. These results are being validated in-vitro. Preliminary immunostaining results showed membranous beta catenin in BPH and that seemed to be more heterogeneous in PC sections. A correlation with CSNK1A1 localization and amount is still to be achieved. Our results suggest a role of CSNK1A1 in the pathogenesis of BPH and PC by working on the proliferation induction axis, and malignant behaviour of cells. Our staining results suggest a minor role of beta catenin and Wnt pathway in these axes from which emerges the need to deeply investigate the pathways in which CSNK1A1 is implicated in BPH and PC initiation and progression.

**Conclusion** Our results suggest an increase in CSNK1A1 in BPH and PC, which flags this protein as a potential marker in the progression of PC. More investigation is needed to verify whether this protein is involved in cancer initiation or in the direct inhibition of the oncogenic Wnt/beta-catenin signalling pathway and other pathways.

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**PO-151**

**NOTCH SIGNALLING DIFFERENTIATES DISEASE-FREE SURVIVAL IN PROSTATE CANCER PATIENTS BY AFFECTING THE EPITHELIAL-TO-MESENCHYMAL TRANSITION-ASSOCIATED PROCESSES**

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**Introduction** In majority of cases tumour of the prostate is developing with benign age-related prostatic hyperplasia. However some of them are very aggressive. Therefore, the dispute how to differentiate patients with malignant vs benign form of the disease and patients, which have risk of recurrence remains open. Notch signalling plays a pivotal role in prostate homeostasis and its deregulation is associated with prostate tumour recurrence through involvement in epithelial-to-mesenchymal transition (EMT). This study aimed to determine role of Notch signalling and its downstream effects in recurrence of prostate cancer and to reveal network of genes that differential expression may be substantially significant for relapse.

**Material and methods** TCGA PRAD cohort was examined regarding expression of Notch receptors and their association with tumour recurrence. DFS analysis was performed using EvaluateCutpoints (log-rank, p<0.05). Global biological differences between DFS groups were provided with GSEA in terms of KEGG pathways (tTest, FDR<0.25) and visualised with BubbleGUM software. Downstream targets of Notch transcription factors (HES/HEY) were obtained from GTGD database. Effects of Notch downstream signalling on disease recurrence were further examined with Multiple Factor Analysis (MFA). Networks were constructed with NetworkAnalyst based on differential expression analysis (FDR<0.1) and STRING confidence score.

**Results and discussions** DFS analysis showed common profile for all Notch receptors with low expression as favourable prognosis. GSEA analyses between favourable/unfavourable expression groups resulted in overrepresentation of gene sets directly involved in EMT (adhesion, integrins, WNT signalling) in unfavourable group. MFA performed on EMT markers showed that their expression clearly differentiates disease relapse from tumour free patients. Finally, network of downstream Notch effectors revealed 745 disease recurrence related genes involved mainly in carcinogenesis-associated processes (cell cycle, apoptosis) and adhesion supporting our primary hypothesis.

**Conclusion** This research revealed the role of Notch in prostate cancer recurrence mechanism. It showed Notch receptors as potential markers indicating risk of disease recurrence. Moreover, downstream Notch signalling tends to affect cell cycle, tissue remodelling and architecture, thus indicating potential to trigger EMT.

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**PO-152**

**DIFFERENTIATION OF LUNG SQUAMOUS CELL CARCINOMA (LUSC) AND LUNG ADENOCARCINOMA (LUAD) BY GENE CO-EXPRESSION ANALYSIS OF NOTCH SIGNALLING TARGETS**

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**Introduction** Lung carcinomas are very aggressive malignancies, which remain leading cancer-related cause of death among men and women worldwide. Regarding histological classification LUSC and LUAD account for the majority of lung tumours among non-small cell carcinomas (NSCLC). Notch signalling is evolutionarily-conserved pathway that regulates many cellular processes such as proliferation, differentiation and epithelial-to-mesenchymal transition (EMT). To date, aberrant Notch
signalling has been linked with wide variety of malignancies, including lung tumours. However the association between co-expression profile of Notch downstream effector and lung cancer subtypes remains unclear. Therefore the aim of our study was to investigate functional gene co-expression networks to search for candidate biomarkers or therapeutic targets.

**Material and methods** In our analysis we used RNASeq expression and clinical data downloaded from The Cancer Genome Atlas (TCGA). Gene Set Enrichment Analysis (GSEA) performed for canonical pathways pointed to Notch pathway as one of the most significant. Subsequently we analysed expression of downstream Notch effectors, 2949 HES/HEY transcription factors targets. To this extent used Weighted Gene Co-expression Network Analysis (WGCNA) to find differences in gene expression profile between LUSC and LUAD.

**Results and discussions** The analysis of Notch pathway downstream targets which expression is regulated by HES/HEY transcription factors, identified 9 gene modules highly correlated with cancer type, with two of them as the most promising. Functional analysis revealed that among the differentially expressed genes were those involved in proliferation, cell cycle regulation, DNA repair, EMT, adhesion and metabolic processes, for example: TP63, PIK3CA, ADAM23, DLG1, FXR1, SENP5, TTK, BIRC5, KIF18A, KIF14, KIF4A, MCM4, MCM10. For one module the highly connected hub gene is TP63, acts as oncogene in many tumour types including squamous cell carcinomas, and for the second module is KIF4A. Interestingly, all listed genes were found to be overexpressed in LUSC and downexpressed in LUAD.

**Conclusion** Our analysis could be valuable for better understanding of the molecular mechanism of lung carcinoma as well as Notch signalling in lung cancer with emphasis of pathway gene expression as useful biomarker for differentiating cancer progression in lung cancer subtypes.

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**PO-153 INVESTIGATING TOBACCO SMOKING DIFFERENTIAL EFFECTS ON LUNG AND BLADDER CANCER**

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**Introduction** Cancer initiation and progression mechanisms contingent upon tobacco use are not yet comprehensively understood. In lung adenocarcinoma (LUAD) increased overall mutation rate was attributed to smoking, whereas in bladder cancer (BLCA) reduced suppression of oncogenes in smokers, might have been a distinguishing factor between cancers caused in smokers and never smokers (NS).

It is well established that cigarette smoking is a risk factor for BLCA. However it is also found that the risk of BLCA as well as LUAD, might be higher in women than in men when both subjects have smoked comparable amounts of cigarettes, whilst confirmed that smoking cessation reduces the risk of BLCA.

Smoking is usually associated with lung cancer however, almost 25% of all lung cancer cases worldwide have been found in NS. Environmental tobacco is a relatively weak carcinogen thus it is a controversial thought to assume that LUAD in NS is due to passive exposure.

**Material and methods** In our analyses we used mRNASeq expression and clinical data downloaded from The Cancer Genome Atlas (TCGA), and to perform differential gene expression analysis we used Gene Set Enrichment Analysis (GSEA). We focused on signalling pathways to investigate the molecular biology of the association of TGF-β, Wnt and Notch to explain their contribution to the inter-individual variations associated with smoking status. We will investigate how these three pathways cross-talk and respond to signals from the microenvironment to regulate the expression and function of epithelial mesenchymal transition (EMT) inducing transcription factors in the development and physiology of both cancers.

**Results and discussions** Of interest our analysis in nonsmokers have showed JAG1 to be underexpressed in LUAD and overexpressed in BLCA contrary to the expression of NOTCH2. Whereas in current smokers ADAM17 as well as PSEN2 have showed underexpression in LUAD but overexpression in BLCA with NOTCH1 presenting a reverse effect.

**Conclusion** Our approach to a pathway specific gene association analysis will help detect the accumulative effect of group of functionally related genes aiding in revealing the transcriptional program accounting for the variability in the phenotype, since cancers arise from the aberrations in multiple genes, several of which have moderate or even less than moderate effects, making them difficult to detect by individual gene analysis.

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