PD65-01
GERMLINE MUTATIONS IN THE KALLIKREIN 6 REGION AND PRE-Disposition FOR AGGRESSIVE PROSTATE CANcer
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INTRODUCTION AND OBJECTIVES: Prostate Cancer (PCa) is a highly heterogeneous disease, ranging from indolent tumors to rapidly progressing life-threatening metastatic disease. There is a need for markers that can specifically identify individuals at increased risk of harboring aggressive forms of PCa.

METHODS: We surveyed the Kallikrein (KLK) region (KLK1-15) for single nucleotide polymorphisms (SNPs) associated with aggressive PCa (defined as Gleason Score ≥ 8) in 1858 PCa patients. Discovery cohorts (Swiss arm of the European Randomized Study of Screening for PCa, n = 379, and Toronto, Canada, Princess Margaret Cancer Centre, n = 540) and a validation cohort (Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial, n = 939) were analyzed. Fine-mapping within the KLK region was carried out by genotyping and imputation in the discovery cohort whereas PLCO data was provided through DbGaP. The influence of SNPs of interest on biochemical free survival was evaluated in an intermediate-risk disease patient cohort from the International Cancer Genome Consortium (ICGC; n = 130) treated for localized PCa and analyzed with next generation sequencing. Single-, multi-SNP association studies, and haplotype analyses were performed. All statistical tests were two-sided.

RESULTS: Several SNPs in very strong linkage disequilibrium in the KLK6 region and located within the same haplotype (rs131640578, rs79324425, rs11666929, rs28384475, rs3810287), identified individuals at increased risk of aggressive PCa in both discovery (OR = 3.51-3.64; 95% CI = 2.01-6.36; p = 1.0 x 10^-8-8.4 x 10^-9) and validation (OR = 1.89-1.96; 95% CI = 0.99-3.71; p = 0.04-0.05) cohorts. The validation cohort revealed another important haplotype with 2 SNPs at the same locus (rs28665094, p = 0.006 and rs268890, p = 0.005) associated with aggressive PCa. The overall test of haplotype association was highly statistically significant in the discovery cohort (p = 3.5 x 10^-7), in the PLCO cohort (p = 0.006) and in the three data sets combined (p = 2.3 x 10^-7). These germline SNPs predicted relapse independently of standard clinical and molecular factors in the ICGC cohort (HR = 3.15, 95% CI = 1.57-6.34 p = 5.001).

CONCLUSIONS: Our fine-mapping study has identified novel loci in the KLK6 region strongly associated with aggressive PCa. Additional sequencing studies might help identify rare variants with major effect in this KLK6 region.

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PD65-02
ONCOSOMES AS A NOVEL LIQUID BIOPSY BIOMARKER FOR QUANTIFYING METASTATIC CANCER DYNAMICS IN REAL-TIME
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INTRODUCTION AND OBJECTIVES: Tumor cells acquire qualities that enable them to succeed at key steps of the metastatic cascade, but very little is known about how individual cells accomplish these feats in a challenging hemodynamically active environment. Using intravital imaging, we observe that oncosome release is a key event during cancer cell extravasation in various prostate cancer cell lines. Oncosomes are large cell fragments released by cancer cells at various stages of cancer progression. Having observed their release in vivo during cancer cell extravasation, we sought to determine what other stages of metastasis oncosomes were released.

METHODS: Using PC-3, LnCAP, Du145 cells, intravenous injection into the choioallantoic membrane (CAM) of chick embryos, a gold standard of visualizing cancer cell extravasation, was employed and confocal resonance scanning microscopy was used to visualize the release of oncosomes and other smaller extracellular vesicles in vivo. Blood at various time points was also collected to enumerate the number of CD9+ve and STEAP1+ve oncosomes released by extravasating cells. Primary tumors were also formed and blood collected in the same manner to ascertain the extent of oncosome release in vivo.

RESULTS: At the key step of extravasation, arrested cancer cells release oncosomes into the microcirculation which are observed to exhibit a diameter >900 nm and expressing surface antigens found on the surrogate prostate cancer cell such as CD9 and STEAP1. We explored the abundance and biophysical characteristics (size diameter range) of extracellular vesicles (EVs) released during the metastatic cascade and found that oncosomes are not consistently released by primary tumors or metastases and that these large cancer cell fragments are specifically released by actively extravasating cancer cells.

CONCLUSIONS: Circulating oncosome levels in patient plasma are a novel biomarker or “liquid biopsy” for actively metastasizing cells in the body, representing a powerful tool for monitoring metastatic cancer dynamics. We show that oncosome biogenesis is a specific byproduct of extravasating cells and not by primary tumors or metastatic deposits even in the presence of pro-apoptotic or pro-necrotic stimuli. Our findings in plasma samples from patients on first-line treatment for metastatic prostate cancer support the concept of oncosomes as a promising biomarker for monitoring cancer metastasis dynamics in real-time, a novel “liquid biopsy” for metastatic prostate cancer treatment response.

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PD65-03
DECIPHER GENE EXPRESSION LEVELS DO NOT CORRELATE WITH PATHOLOGIC FEATURES OF AGGRESSIVE PROSTATE CANCER IN AFRICAN AMERICANS
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INTRODUCTION AND OBJECTIVES: Genomic testing is used with increasing frequency as part of a personalized approach to managing prostate cancer. Decipher is one such test that analyzes the expression of 22 RNA biomarkers from archival prostate tissue and predicts risk of metastatic progression and prostate cancer specific mortality. The company also provides microarray analysis to characterize additional markers from the Decipher Genomic Resource Information Database (GRID) that have been implicated in prostate cancer. Traditionally, adverse pathologic features at prostatectomy have been