International Conference on
GASTROINTESTINAL CANCER AND THERAPEUTICS
&
4th World Congress on
DIGESTIVE & METABOLIC DISEASES
&
26th Annual Congress on
CANCER SCIENCE AND TARGETED THERAPIES
October 29-30, 2018 | San Francisco, USA

Large chromosomal rearrangements yield biomarkers to distinguish low-risk from intermediate and high-risk prostate cancer

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Background: We tested the hypothesis that chromosomal rearrangements (CRs) could separate low-risk of progression (LRP) from an intermediate and high risk of progression (IHRP) prostate cancer (PCa), and if these CRs have the potential to identify men with LRP on needle biopsy that harbor IHRP PCa in the prostate gland.

Methods: Mate Pair sequencing of amplified DNA from pure populations of Gleason patterns (GPs) in 154 frozen specimens from 126 patients was used to detect CRs. A custom bioinformatics pipeline identified abnormal junctions and copy number variations (CNVs). Chromosomal instability was approximated by the number of abnormal junctions. Potential CR biomarkers with the higher incidence of IHRP than in LRP and having significance in PCa biology were identified. Independent marker validation was performed by FISH in a set of 152 archived specimens from 124 patients.

Results: The number of abnormal junctions did not distinguish LRP from IHRP. Loci corresponding to genes implicated in PCa were more frequently altered in IHRP. Integrated analysis of CNVs and microarray data yielded six potential markers that were more frequently detected in the GP3 of a Gleason score of 7 (GS7) PCa compared to GP3 in a GS6 PCa. Five of those were cross-validated in an independent sample-set with statistically significant AUCs. Probes detecting deletions in PTEN and CHD1 had AUCs of 0.87 and 0.73, respectively, and probes detecting gains in ASAP1, MYC, and HDAC9 had AUCs of 0.71, 0.82, and 0.77, respectively.

Conclusions: CNVs in regions encompassing important PCa genes were predictive of cancer significance and have the potential to identify men with LRP PCa on needle biopsy who have IHRP PCa in their prostate gland.

Biography

Farhad Kosari's interests are in the discovery and development of clinically relevant biomarkers for cancers. His domains of expertise are bioinformatics and molecular biology particularly as related to the development of biomarker-based assays. His recent projects related to the identification of genomic abnormalities that distinguish "indolent" from "significant" prostate cancers which is one of the most urgent needs in the clinical management of patients with PCa. His interests also include neuroendocrine (NE) tumors of the lung including small cell lung cancers (SCLC) and adenocarcinomas with NE differentiation (ND-AD). Characterized by the expression of ASCL1, ND-AD is a sizable subset of lung tumors that are largely understudied and underappreciated. Kosari's group has recently discovered the main drivers of ND-AD and is testing targeted therapies in patient-derived tumors. Furthermore, he has recently identified anti-tumor immunity as the key determinant of survival in SCLC and is currently investigating the therapeutic implications of these findings.

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