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Driver Gene Networks of Genomic Instability in Prostate Cancer Progression

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Abstract

Prostate cancer (PC) is a major leading cause of death in men in US. Genomic rearrangement, copy number changes, and increased mutational burden are well characterized features that correlate highly with PC progression. These genomic alterations frequently co-occur with specific oncogene mutations that are capable of altering gene expression and promoting other genomic abnormalities. The Cancer Genome Atlas (TCGA) project reported comprehensive genomic and epigenomic profiles in PC to identify disease associated molecular alterations. However, drivers of genomic instability (GI) and their relationships in PC progression are elusive. We developed an integrated scoring method for GI in PC (PCGI) that encompasses broad and focal copy number alterations (CNA), genomic rearrangements, microsatellite instability (MSI), and somatic mutational burden. Devising this novel PCGI scoring method, we identified seven drivers of GI that significantly correlated with PCGI score. Analysis of mutual exclusivity and co-occurrence between the drivers we discovered revealed SPOP and TP53 mutations to be mutually exclusive in 3,597 PC genomic profiles from PC patients. We also could assign co-occurring drivers to one of two networks linked separately to SPOP-network and TP53-network. Recent studies suggest that tumors harboring genomic alterations are significantly associated with gene expression phenotypes linked with PC subtypes and loss/gain of function mutations of genetic drivers have been associated with a characteristic transcriptional phenotype. We thus examined whether the transcriptional architecture of PC, within the guidance of PCGI, can be applied to a series of clinical contexts, including radical prostatectomy samples, prostate diagnostic needle biopsy samples, and CTCs from patients with metastatic castration resistant PC. This identifies potential links from the genetic alterations to secondary oncogenic driver activations resulting in a large number of transcriptional changes. The GI driver networks can distinguish disease subtypes which are related to GI events relevant to disease progression such as metastasis.