**Understanding the molecular biology of prostate cancer in the context of other cancers through pan-cancer genomic analyses**

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Background: The Cancer Genome Atlas (TCGA) project has provided a comprehensive genomics data resource for 32 cancer types, including of 498 prostate cancers, as characterized by multiple molecular analytical platforms. These data—including mRNA, miRNA, protein, DNA methylation, copy number, somatic mutation, and structural variation—provide a common platform for the study of prostate cancer in the molecular context of other diverse cancer types. Subsequent to the TCGA consortium-led "marker" study of primary prostate cancer (TCGA Network Cell 2015), my group has initiated several independent "pan-cancer" genomic studies of TCGA data, which involve further defining genomic aberrations and molecular subtypes of the TCGA prostate cancer cases.

Methods: We developed an alternative approach to the molecular classification of cancers from different types, whereby the molecular patterns representing tissue or histologic dominant effects are first removed computationally, with the resulting classes representing emergent themes across tumor lineages. We applied this approach, first in a "pan-urologic" study (Chen, et al. Nature Communications 2017) involving all 1954 urologic cancers (bladder, kidney, prostate, and testicular), and then in a subsequent "Pan32" study (Chen, et al. Clinical Cancer Research 2018) involving all 32 cancer types and 10,224 cases. In a separate study (Zhang, et al. Cancer Cell 2017), we carried out a proteogenomic analysis focusing on PI3K/AKT/mTOR pathway across 11,219 human cancers. We also carried out integrative analysis of structural variation (by whole-genome sequencing) and gene expression data from 1,448 cancers involving 18 histopathological types, including 116 prostate cancers (Zhang et al., Cell Reports 2018).

Results: Immune checkpoint pathway markers and molecular signatures of immune infiltrates were most strongly manifested within a pan-cancer molecular class representing ~15% of prostate cancers. Pathway-level differences involving hypoxia, NRF2-ARE, Wnt, and Notch were manifested in two additional classes (representing ~18% of prostate cancers) enriched for mesenchymal markers and miR-200 silencing. Within specific mutated genes of PI3K/AKT/mTOR pathway (e.g. *PIK3CA*, *PTEN*), frequency, mutation hotspot residues, in silico predictions, and functional assays were all informative in distinguishing the subset of genetic variants more likely to have functional relevance. A substantial fraction of prostate cancers showed high mTOR pathway activity without an associated canonical genetic or genomic alteration. We identified hundreds of genes for which the nearby presence (within 100 kb) of a somatic structural variant breakpoint is associated with altered expression.

Conclusions: Our pan-cancer analyses provide an excellent framework for examining pathways or processes that would cut across individual cancer types.

Conflict of Interest: None

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