Commentary

Distinct Genomic Alterations in Prostate Tumors from African American Men

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The advancement of next generation sequencing (NGS) has made possible large scale tumor molecule profiling and thus, the molecular classification of tumor subtypes. The Cancer Genome Atlas (TCGA) has been successful in publishing many important discoveries elucidating the mutation landscape, including the recent Cell article (Cancer Genome Atlas Research Network. Electronic address, s.c.m.o. and Cancer Genome Atlas Research, N., 2015), where at least seven molecular subtypes were proposed for prostate tumors. Although it is well known that both incidence and mortality are substantially higher in men of African ancestry, most prostate tumor molecular profiling studies have been conducted on men of European ancestry (Baca et al., 2013; Robinson et al., 2015). In this issue of EBioMedicine, Petrovics et al. (2015) reported distinctly different spectrums of genomic alterations in prostate tumors between African American (AA) and Caucasian American (CA) men. Such in-depth research focusing on racial differences adds more insights into our understanding of molecular carcinogenesis and tumor heterogeneity for prostate cancer.

The key finding of this current study by Petrovics et al. is novel prevalent deletion of 3q13.31 locus centering on LSAMP gene in AA prostate cancer tumors, especially those likely to lead to recurrence or progression. Such a mutation could potentially be used as a valuable treatment target and/or prognostic biomarker in clinical setting with further confirmation and studies of its role in prostate tumor biology. Local ancestry analysis in this genomic region is also likely to advance our understanding on the underlying mechanism leading to differential somatic alterations between prostate cancer patients of European and African ancestry. In addition, significantly higher frequency of inter-chromosome rearrangements, a phenomenon called “chromoplexy” (Baca et al., 2013), was also observed in prostate tumors from AA as compared to CA men in this study. Higher prevalence of the signature deletion of LSAMP gene and inter-chromosome rearrangements may explain some of the observed health disparity of prostate cancer in AA population.

The study by Petrovics et al. provided a paradigm for studying other cancer types with large racial or ethnic difference in prevalence and/or disease severity. Along this line, a recent study based on TCGA data alone was conducted in comparing the genomic landscape of breast cancer between AA and CA women and suggested more aggressive tumor biology in AA than CA (Keenan et al., 2015). One notable aspect of Petrovics et al.’s findings is that recurrent prostate cancer driver mutations, such as those involved in either PTEN or ERG genes, commonly observed in CA men, are less frequent in AA men. Such information may be useful in developing and applying the targeted therapeutics for patients with different ethnic background. Remarkably lower frequency of PTEN loss in AA prostate cancer patients would make the therapeutics targeting loss of PTEN less likely to be successful in treating AA patients with prostate cancer.

Tumor genomic profiling and molecular subtyping is critically implicated in the new Precision Medicine Initiative (PMI) called upon by President Obama, however, investigations of genetic predisposition and population risk stratification are equally important. The new Precision Medicine Initiative (PMI) specifically calls for the enrollment of under studied populations including AA. The multiethnic cohort (MEC) study has suggested that the underlying genetics play a greater role in explaining racial/ethnic differences in prostate cancer risk than lifestyle factors (Park et al., 2015). For the germline susceptibility, both difference and commonality were observed and highlighted by assessing the genetic risk loci originally discovered in CA in the AA population (Haiman et al., 2011). Moving forward, the integration of both germline (for susceptibility) and somatic (for progression) genomic data will open up a new venue in searching for germline-somatic continuums in understanding of tumorigenesis and development of personalized cancer medicine (Pujana, 2014; Feigelson et al., 2014).

Petrovics et al. demonstrated that the statistical power can be improved by combining and integrating different data types including whole genome sequencing (WGS), FISH assays and SNP array data. Despite the initial discovery was based on only 7 CA and 7 AA tumor/normal pairs of WGS data, the findings of LSAMP deletion were further replicated in 1) TCGA SNP array data for 279 CA and 41 AA patients; and 2) FISH assay data for 59 CA and 42 AA. Even larger sample size, especially for the discovery phase, could possibly lead to additional novel findings highlighting differences in prostate tumors between CA and AA patients.

More comprehensive and systematic research is needed in order to further advance our understanding of the tumor heterogeneity among worldwide populations for prostate and other cancers. As NGS becomes...
more routine in clinical and research laboratories, somatic lesions identified by sequencing the cancer genome will certainly improve the personalized treatment and clinical management for the cancer patient. In the meantime, the reportable pathogenic germline mutations identified by sequencing the paired normal tissue or blood samples could prompt the genetic screening of the family and relatives for cancer or disease predisposition and subsequent prevention to realize the promise of precision medicine in the very near future.

Disclosure

The author declared no conflicts of interest.

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