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Identification of Genomic Mutations in Prostate Cancer and Cancer Stem Cells By Single Cell RNAseq Analysis

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Abstract : Background: Genetic mutations are highly associated with increased prostate cancer risk. In addition to whole genome sequencing, somatic mutations can be identified by aligning transcriptome sequences to the human genome. Here we analyzed bulk RNAseq and single cell RNAseq data of human prostate cancer cells and their matched non-cancer cells in benign regions from 4 individual patients. Methods: Sequencing raw reads were aligned to the reference genome hg38 using STAR. Variants were annotated using Annovar with respect to overlap gene annotation information, effect on gene and protein sequence, and SIFT annotation of nonsynonymous variant effect. We determined cancer-specific novel alleles by comparing variant calls in cancer cells to matched benign cells from the same individual by selecting unique alleles that were only detected in the cancer samples. Results: In bulk RNAseq data from 3 patients, the most common variants were the noncoding mutations at UTR3/UTR5, and the major variant types were single-nucleotide polymorphisms (SNP) including frameshift mutations. C>T transversion is the most frequently presented substitution of SNP. A total of 222 genes carrying unique exonic or UTR variants were revealed in cancer cells across 3 patients but not in benign cells. Among them, transcriptome levels of 7 genes (CITED2, YOD1, MCM4, HNRNPA2B1, KIF20B, DPYSL2, NR4A1) were significantly up or down regulated in cancer stem cells. Out of the 222 commonly mutated genes in cancer, 19 have nonsynonymous variants and 11 are damaged genes with variants including SIFT, frameshifts, stop gain/loss, and insertions/deletions (indels). Two damaged genes, activating transcription factor 6 (ATF6) and histone demethylase KDM3A are of particular interest; the former is a survival factor for certain cancer cells while the later positively activates androgen receptor target genes in prostate cancer. Further, single cell RNAseq data of cancer cells and their matched non-cancer benign cells from both primary 2D and 3D tumoroid cultures were analyzed. Similar to the bulk RNAseq data, single cell RNAseq in cancer demonstrated that the exonic mutations are less common than noncoding variants, with SNPs including frameshift mutations the most frequently presented types in cancer. Compared to cancer stem cell enriched-3D tumoroids, 2D cancer cells carried 3-times higher variants, 8-times more coding mutations and 10-times more nonsynonymous SNP. Finally, in both 2D primary and 3D tumoroid cultures, cancer stem cells exhibited fewer coding mutations and noncoding SNP or insertions/deletions than non-stem cancer cells. Summary: Our study demonstrates the usefulness of bulk and single cell RNAseaq data in identifying somatic mutations in prostate cancer, providing an alternative method in screening candidate genes for prostate cancer diagnosis and potential therapeutic targets. Cancer stem cells carry fewer somatic mutations than non-stem cancer cells due to their inherited immortal stand DNA from parental stem cells that explains their long-lived characteristics.

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