⇥ **PROSTATE CANCER**

Evolutionary and clinical trajectories of early-onset prostate cancer

> *the study offers insight into the earliest mutational events … in prostate cancer*

Deciphering the earliest somatic alterations in prostate cancer can yield invaluable insight into temporal evolutionary and clinical trajectories to inform risk stratification. However, most prior studies have focused on late-onset disease, hindering identification of such early events. Using an integrative genomic approach in early-onset prostate cancer (EOPC), a new study published in *Cancer Cell* has uncovered an enzymatic mutational process driving acquisition of the earliest mutations in prostate cancer and developed a statistical model to predict the order of somatic events and associated outcomes.

To examine the relationship between somatic alterations and age at diagnosis, the international team of investigators performed comprehensive genomic profiling in 292 patients, including 203 with EOPC (age of diagnosis ≤55 years). The analysis revealed distinct patterns of age-related recurrent breakpoint hot spots,

termed recurrent genomic alterations (RGAs), in EOPCs that were consistent with a primarily clonal origin, including a clinically relevant RGA at 8q22. The 8q22 region displayed recurrent genomic duplications of *ESRP1*, which encodes an RNA-binding protein involved in epithelial–mesenchymal transition and RNA splicing. Importantly, tissue microarray analysis ($n = 11,954$) revealed that high ESRP1 immunostaining correlated with high proliferation index, Gleason score, tumour stage, nodal metastasis burden and preoperative PSA levels, as well as short time to biochemical recurrence (BCR). Further multivariate analysis established ESRP1 as an independent prognostic marker.

Genome-wide analysis also revealed an APOBEC-associated mutational signature that exhibited a clock-like temporal pattern of mutation accumulation. APOBEC-associated mutations were enriched at C/G (kataegis) clusters, which commonly lead to localized hypermutation. Moreover, kataegis events — primarily those attributable to APOBEC3 — were associated with patient age and frequently colocalized with breakpoints, including RGAs resulting in driver gene alterations. The findings suggest that APOBEC3 drives an endogenous, age-associated mutagenic process responsible for clock-like accumulation of early somatic mutations in prostate cancer.

Next, methylation arrays and RNA sequencing were used to investigate cell type composition and gene expression patterns in EOPC. To this end, the authors developed and validated the purity-adjusted

epigenetic prostate cancer index (PEPCI), a methylation-based score estimating the cell type composition and clinical aggressiveness of each tumour. Integrated analysis of PEPCI scores and CLICK cluster signatures — based on CLICK, a clustering algorithm for gene expression data with prognostic value — revealed four distinct molecular subgroups with distinct cell composition and transcriptional signatures that were associated with clinical outcome. Clinical validation in The Cancer Genome Atlas (TCGA) cohort ($n = 462$) showed that the subgroups could predict BCR in patients with intermediate-risk Gleason score 7, demonstrating prognostic potential.

The authors leveraged the enrichment for early somatic alterations and the high clonality of their EOPC cohort to develop PRESCIENT (prediction of sequential changes in the evolution of nascent tumours), a statistical model that uses molecular markers to predict the temporal order of somatic events and the associated probability of event-free survival. Importantly, PRESCIENT could predict outcomes and the next alteration in a cohort of 40 patients with local metastasis and was more accurate than frequency-based models.

Overall, the study offers insight into the earliest mutational events and evolutionary trajectories in prostate cancer and expertly demonstrates how such knowledge can be integrated into a framework for prognostication.

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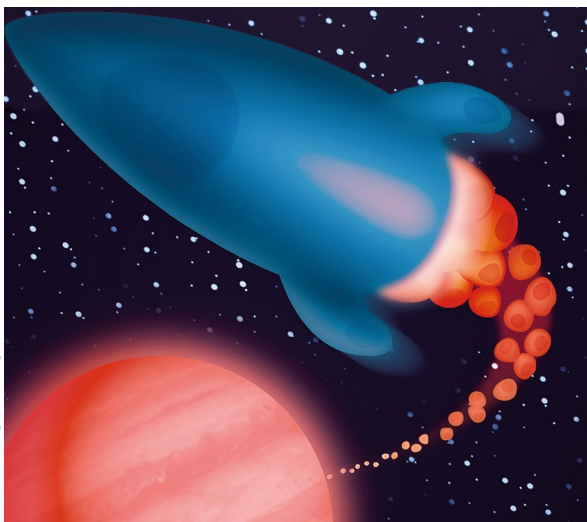
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