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PROSTATE CANCER

The importance of the mitochondrial genome

An analysis of the mitochondrial genome of patients with prostate cancer shows that mutations in mitochondrial DNA are frequent and associate with nuclear DNA mutations. In addition, mitochondrial mutations were shown to correlate with risk of biochemical relapse after definitive treatment.

"Much attention has been given to the nuclear genome of patients with localized or metastatic prostate cancer, which led to identification of drug candidates and biomarkers," Paul Boutros, senior author of the study, told *Nature Reviews Urology*. "By contrast, the mitochondrial genome has not been well studied. We wanted to understand whether mutations in the mitochondrial genome might explain some of the differences in patient survival we see in the clinic."

The team analysed data from 384 tumours classified as early-onset (age at diagnosis <50 years) or late-onset disease. The late-onset patients comprised low-risk, intermediate-risk and high-risk groups. Overall, the researchers identified 293 mitochondrial single-nucleotide variants (mtSNVs); 47.4% of tumours had ≥1 mtSNVs and 6.8% had ≥3 mtSNVs. The mitochondrial non-coding control region was most frequently mutated (15.4% of tumours). In addition, 157 and 22 mtSNVs were found in mitochondrial protein-coding genes and tRNA genes, respectively. Patients with early-onset disease were significantly more likely to have no mitochondrial mutations than those with late-onset disease ($P = 4.22 \times 10^{-10}$), but distribution of mtSNVs across the mitochondrial genome was similar between the groups.

The team also evaluated associations between mtSNVs (22 features) and mutations in the nuclear genome (40 somatic driver events). They discovered, for example, that SNVs in *FOXA1* and *MED12* were positively correlated with multiple mitochondrial features. In addition, mutations in the mitochondrial origin of heavy-strand replication (OHR) region co-occurred with copy number gains of genomic *MYC*. In patients who had both of these aberrations, the risk of biochemical failure after primary radiotherapy or surgery was significantly higher than that of those who had neither or only one of the mutations. According to the researchers, this and similar findings for other combinations suggest a synergistic mitochondrial–nuclear effect on disease aggression, which might be a common phenomenon in prostate cancer.

Finally, the researchers tested whether mitochondrial somatic mutational features were independently prognostic for disease aggression. In hypervariable region 1, mtSNVs were associated with better patient outcome (HR 0.28, 95% CI 0.08–0.9), whereas mtSNVs in the OHR region were associated with worse patient outcome (HR 2.47, 95% CI 1.13–5.38). A signature comprising multiple mtSNVs was able to identify patients at elevated and low risk of biochemical failure.

"Our next step is to evaluate the clinical and translational importance of these mitochondrial mutations in very large cohorts," concludes Boutros. "This research will enable us to really understand how the interplay of nuclear and mitochondrial mutations jointly drives disease aggression and to develop and validate biomarkers that might be clinically useful for stratifying therapy."

Clemens Thoma

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