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PROSTATE CANCER

Analysis of circulating tumour DNA could guide therapy

Treatment drives the dynamic evolution of different cell clones in the primary tumour and metastases, determining therapy resistance in prostate cancer, according to new research published in *Science Translational Medicine*. To date, it was unclear whether the development of lethal prostate cancer is dominated by a single cell clone with a specific set of mutations.

The team of researchers used targeted deep-sequencing to study genomic aberrations in samples from patients with *ERG*-activated castration-resistant prostate cancer who received abiraterone. Specifically, the analysis included estimation of the circulating abundance of tumour clones harbouring point mutations and copy number changes, using novel computational models to interpret sequence data from single-nucleotide polymorphisms in regions with deletions and mutations calling in the coding exons of *SPOP*, *TP53*, *FOXA1*, *PTEN* and other chromosomal regions. "As prostate tumour biopsies are challenging and an invasive and often uncomfortable procedure for the patient, we used tumour DNA circulating in plasma to extract genetic information about the cancer at multiple sequential time-points during the course of the disease," explains Gerhardt Attard, one of the senior investigators of the study. "We evaluated both genomic changes that are common and clonally dominant in early disease and late changes associated with drug resistance." Unlike single-core biopsy, this strategy enabled the assessment of mutation patterns over the course of the disease integrating information from the tumour and distant metastases.

Indeed, the clonal architecture of circulating DNA changed over time. "The abundance of genomic aberrations relative to each other changed continuously, suggesting the presence of multiple clones with distinct genetic changes that were differentially represented in circulation," highlights Attard. The investigators were particularly interested to understand how treatment influenced these dynamics. "In patients progressing on endocrine agents and glucocorticoids, we observed the emergence of resistant clones harbouring mutations in the androgen receptor that were activated by glucocorticoids; hence, drugs like prednisolone and dexamethasone could cause acquired resistance," reports Attard. Interestingly, in patients resistant to antiandrogen treatment, the researchers observed an association between *AR* copy number gain and resistance, but *AR* mutations were not present in all expanding cell clones, suggesting that treatment resistance in a single patient can develop through multiple mechanisms that result in reactivation of androgen receptor signalling.

"There is an urgent need to understand the mechanisms of drug resistance and to characterize patients' cancers to enable better treatment selection," explains Attard. "These studies are now being used to make treatment decisions in prospective clinical trials to confirm that changing treatment based on information from circulating tumour DNA can improve patient outcomes."

Clemens Thoma

Original article Carreira, S. *et al.* Tumor clone dynamics in lethal prostate cancer. *Sci. Transl. Med.* **6**, 254ra125 (2014)