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GENETICS

Tracking clonal origin of prostate cancer

Much controversy surrounding the overtreatment of men with prostate cancer has heightened the need to better understand the key features of the primary tumour and its metastatic progression.Considerable heterogeneity exists among primary prostate tumours, but distant metastases from different anatomical sites share common mutations. Srinivasan Yegnasubramanian and coauthors have now "tracked the clinical, pathological and molecular evolution of prostate cancer over an 18-year period, spanning the initial diagnosis and treatment, through disease recurrence and progression to the development of lethal metastases that were studied after biopsy."

A man aged 47 with prostate adenocarcinoma had his entire primary tumour and involved lymph node removed by radical prostatectomy. He experienced recurrence shortly after his primary therapy, and was treated sequentially with various conventional and experimental therapies including androgen ablation, chemotherapy and radiotherapy. Despite these treatments, 17 years after initial presentation, the patient died of castration-resistant prostate cancer. Tissue samples from seven of his metastatic sites were obtained by autopsy and whole-genome sequencing was carried out on three distinct metastases.

Perhaps unexpectedly, the researchers found that the lethal clone arose from a small, low-grade cancer in the primary tumour, rather than from the surrounding higher-grade primary cancer or resected lymph-node metastases. Alterations in *TP53* and *PTEN* were detected in the primary clone and in progressive subclones.

The study identifed the portion of the primary tumour that seeded a micrometastasis that escaped initial therapy, giving rise to subsequent lethal metastases. These findings underscore the challenges in identifying the primary that ultimately gives rise to lethal disease.

Yegnasubramanian and his team plan to "carry out similar analyses in a larger series of cases to follow the constellation of clinical, pathological and molecular characteristics of prostate cancer using longitudinal sampling of cancer tissues throughout the disease course."

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Original article Haffner, M. C. *et al*. Tracking the clonal origin of lethal prostate cancer. *J. Clin. Invest.* **123**, 4918–4922 (2013)