PROSTATE CANCER

Painting the genetic landscape of prostate cancer

Two whole-exome studies have revealed previously unknown genetic mutations common in prostate cancer. The first study examined primary tumours, whereas the second looked at tumours from men who had died of castration-resistant prostate cancer (CRPC). This stage distinction is important because prostate cancer can have a long disease course with different genetic drivers for early-stage disease compared with CRPC.

In their study of 112 treatment-naïve primary tumours and matched normal tissue samples, Barbieri *et al.* identified more than 5,000 somatic DNA mutations unique to the prostate cancer samples. Examining the nonsilent mutations in more detail, they found several genes known to be implicated in tumorigenesis, such as *TP53*, as well as others that include *FOXA1*, *MED12*, *THSD7B*, *SCN11A* and *ZNF595*, none of which have hitherto been shown to undergo somatic alteration in prostate cancer.

Barbieri *et al.* then went on to study mutations in *SPOP*—the gene that they identified as being most frequently mutated. *SPOP* encodes an E3 ubiquitin ligase and was mutated in 6–15% of 300 tumour samples (from localized to advanced-stage disease). All the mutations affected residues in the enzyme's substrate-binding cleft and are, therefore, biologically significant. Interestingly, *SPOP* mutations were found to be mutually exclusive from *ETS* family gene fusions and translocations, which occur in more than 50% of prostate cancers. Thus, *SPOP* mutation might be a distinct driver of carcinogenesis, diverging from *ETS* family gene alterations early in the disease course.

Tumours that are negative for *ETS* gene family fusion were further characterized in a second study by Grasso and colleagues,

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who studied 50 tumour samples from heavily-pretreated men and 11 high-grade localized, untreated prostate cancers. They identified that focal deletions or mutations of *CHD1* (which encodes an ATP-dependent chromatin-remodelling enzyme) are significantly associated with tumours that do not exhibit *ETS* family gene alterations ($P < 0.0001$).

Although a low level of mutations was identified overall (2.00 per megabase), Grasso *et al.* identified several recurrent mutations in the heavily treated tumours, three of which have never before been implicated in prostate cancer (*MLL2*, *OR5L1* and *CDK12*). The researchers went on to show that *MLL2* (also involved in chromatin remodelling) is associated with the androgen receptor. Furthermore, they showed that mutated *FOXA1*, which occurs in 3.4% of prostate cancers, represses androgen signalling and promotes tumour growth—a novel

androgen-receptor signalling mechanism deregulated in this cancer.

With these studies, we now have a clearer picture of the prostate cancer genetic landscape, from early-stage to castration-resistant disease. The next logical step is to exploit this information to benefit patients. “We intend to use these studies as a basis and rationale for studying serial biopsies on patients with metastatic prostate cancer as they undergo therapy,” explained investigator Kenneth Pienta. In doing so, new targets for therapeutic development as well as personalized treatment might be identified.

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Original articles Barbieri, C. E. *et al.* Exome sequencing identifies recurrent *SPOP*, *FOXA1* and *MED12* mutations in prostate cancer. *Nat. Genet.* 44, 685–689 (2012) | Grasso, C. S. *et al.* The mutational landscape of lethal castration-resistant prostate cancer. *Nature* doi:10.1038/nature11125