A Bird's Eye View of Advanced Prostate Cancer

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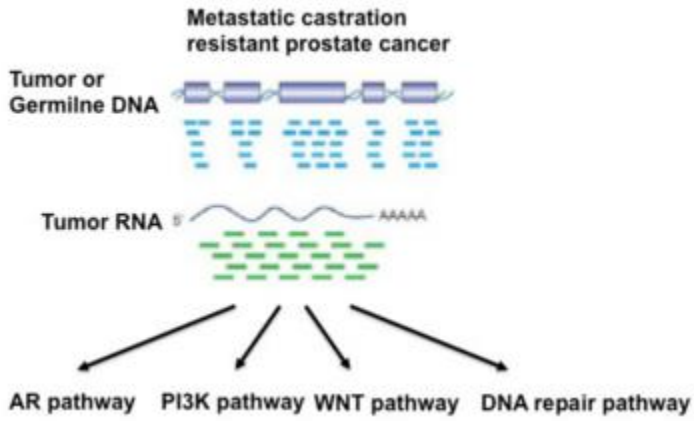

A multi-institution integrative sequencing analysis of DNA and RNA from 150 metastatic, castration resistant prostate cancers reveals both known and novel cancer pathways that are clinically actionable, an important step towards precision medicine.

Image adapted from the publication.

An estimated 220,000 American men are diagnosed with prostate cancer each year, with 30,000 expected to die of it this year. While androgen deprivation therapy (ADT) is initially effective against metastatic disease, most men develop tumors that ultimately become resistant to ADT, including the most recent ADT regimen (abiraterone acetate and enzalutamide). This condition is known as metastatic castration-resistant prostate cancer (mCRPC). While many studies have cataloged somatic alterations in primary prostate cancers, genomic studies of mCRPC have been limited to either autopsy samples or preclinical models. To address the gap in our understanding of mCRPC, an international and multi-institutional consortium that included Fred Hutch investigators and benefitted from key contributions from Dr. Pete Nelson's Laboratory (Human Biology, Clinical Research and Public Health Sciences Divisions), sequenced the DNA and RNA from biopsies of bone or soft tissue metastases prospectively from 150 mCRPC affected individuals. This work was recently published in the journal *Cell*.

This integrative analysis represented an entry point of ongoing clinical trials on combination therapy in mCRPC. The biopsies were obtained from lymph nodes (42%), bone (28.7%), liver (12.7%) as well as other soft tissues (16.7%). Compared to primary prostate tumors, mCRPCs were enriched for mutations in the Androgen Receptor (*AR)* and the tumor suppressor *TP53*. Based on both biological and statistical criteria, mCRPCs could be subdivided into discrete molecular subtypes. These subtypes were grouped based on knowledge of biological pathways and alteration clustering

and included, among others, the PI3K pathway, WNT pathway, DNA repair pathway and the cell cycle machinery. Accordingly, genes that were most frequently altered were *AR* (62.7%), genes encoding ETS family transcription factors (56.7%), *TP53* (53.3%) and *PTEN* (40.7%). Importantly, the metastases of most mCRPC cases harbored alterations deemed to be clinically actionable, meaning that they have either diagnostic or prognostic significance or that they predict therapeutic response.

The AR signaling pathway was found to be altered in 73% (107/150) of cases, either by mutation in *AR* itself, or in regulators of AR signaling such as the *NCOR1/2*, *SPOP* and *ZBTB16* genes. Because most mCRPCs have AR pathway mutations, they are likely to be dependent on AR for viability. As such, future studies may be able to link specific *AR* mutations to clinical outcomes. Additionally, while mutations in the PI3K pathway are well described in cancer, this study uncovered novel alterations in the catalytic subunit *PIK3CB*, suggesting that patients with *PIK3CB* alterations may benefit from PIK3CB-specific inhibitors.

Additionally, 19/150 (12.7%) cases harbored alterations in *BRCA2*, that encodes a DNA repair protein best known for its role in inherited breast and ovarian cancer. This prompted further examination of the DNA repair pathway, which revealed alterations in other well-known DNA repair genes, such as *BRCA1* an *ATM*. Interestingly, previous work has demonstrated that cancers with DNA repair mutations might be particularly sensitive to poly ADP ribose polymerase (PARP) inhibitors. Overall, this study demonstrates that prospective genomics of advanced metastatic prostate cancer is not only feasible, but also enabled discovery of novel mutations that had not been observed in multiple prior studies of primary prostate tumors. Finally, this work suggests that prospective genomics of metastatic disease in treated individuals could potentially be applied to other types of cancer. "We were quite excited to find that a majority of metastatic castration resistant prostate cancers (mCRPC) harbor actionable mutations. The findings suggest there is potential clinical utility of genetic testing to guide optimal therapy in the setting of mCRPC. For example, a large number of cases had either somatic or germline DNA repair pathway alterations which may be predictive of favorable response to platinum or PARP inhibitor therapy," said Dr. Colin Pritchard, a UW investigator involved in the study.

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