“N of 1” case reports in the era of whole-genome sequencing

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Commentary

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Prostate cancer has a range of clinical outcomes, from complete remission in response to treatment or death as a result of aggressive metastasis. Prognosis for individuals with prostate cancer is not readily predictable, and new diagnostics will be useful for treatment strategy determination. In this issue of the JCI, Haffner and colleagues use comprehensive tumor genome sequencing to investigate the origin of genetic mutations underlying a case of lethal prostate cancer. Surprisingly, the lethal clone in this individual arose from a tumor focus that is typically considered very low risk based on histology. Their report highlights the need to collect and curate “N of 1” cases to develop a database that can be used for clinical decision making.

The case of the lethal clone

Scientists are detectives at heart. When Haffner and colleagues learned about a case of lethal metastatic prostate cancer with evidence dating back 17 years, they had to take the case (1). Using an approach similar to one previously employed to follow pancreatic cancer progression (2), the authors began with comprehensive genome sequencing of metastatic tumor deposits recovered at autopsy. This analysis yielded evidence of mutations in several well-documented prostate cancer genes, such as tumor suppressor PTEN, tumor protein p53 (TP53), speckle-type POZ protein (SPOP), ATP-dependent helicase (ATRX), and androgen receptor (AR) (1), all of which are known to be recurrently altered in end-stage, castration-resistant prostate cancer. Because this patient’s primary tumor had been surgically excised (and saved) 17 years earlier, the authors had a unique opportunity to ask the “whodunit” question. Which, if any, of these mutations were present in the primary tumor? How did this constellation of mutations evolve over time as the patient suffered multiple relapses (with accompanying tissue biopsies) during 17 years of treatment with various interventions? Answering these questions offered the potential for new insights into prostate cancer progression, drug resistance mechanisms, and perhaps opportunities to develop molecular diagnostics.

Histological examination of the primary tumor revealed multiple regions of high-grade (Gleason 4) tumor, a small focus of lower-grade (Gleason 3) disease, and a single lymph node metastasis (1). It is well established that patients with high-volume, high-grade primary disease have an increased risk of recurrence; therefore, this patient’s subsequent clinical course of metastatic prostate cancer is not surprising. It was surprising that the lethal clone, defined by the presence of the same PTEN, TP53, and SPOP mutations recovered at autopsy, originated from the small, low-grade Gleason 3 focus, and not from the much more substantial, high-volume Gleason 4 tumors, which did not harbor PTEN,
everolimus treatment. Despite the small number of patients, this report provided enough evidence for the commercial sponsor to initiate a new clinical trial of everolimus in TSC1 mutant cancers, regardless of histology. Such biomarker-based clinical trials (called “basket studies”) are becoming increasingly common in oncology and reflect growing confidence that molecular diagnostics can predict treatment response.

Future detective work
To harness the potential effect of these anecdotes on a larger scale, the National Cancer Institute recently announced the Exceptional Cases Initiative to identify and sequence the tumors from 100 extraordinary responders to any form of cancer therapy (5). If successful, this initiative could legitimize a new field of “N of 1” science. Should we also consider an initiative of “diagnosis-to-death” autopsy cases with longitudinal genomic analysis of tumor progression, as in the example reported here (1)? Such a project would be the 21st-century version of a much older, highly successful “initiative” led by William Osler and colleagues in the late 19th century, when autopsies were routinely performed and yielded new insights into disease pathophysiology. Importantly, these autopsies were not just a series of independent case studies. Only through the collection and
Antifibrotic vitamin D analogs

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Chronic kidney disease is associated with progressive kidney fibrosis, which disrupts normal kidney function. There is a great need for treatments to reduce renal fibrosis. In this issue of the *JCI*, Ito and colleagues report the development of synthetic ligands of the vitamin D receptor that target the TGF-β–SMAD signaling pathway, which is known to regulate fibrosis-associated gene expression, without inducing VDR-associated genes. These ligands ameliorated renal fibrosis in two different mouse models. This study justifies further investigation of these and related compounds for treatment of humans with chronic kidney disease or other diseases characterized by fibrosis.

TGF-β signaling promotes chronic kidney disease

Chronic kidney disease (CKD) affects approximately 10% of the adult population in the developed world (1). A dominant feature of most forms of CKD is the development of kidney fibrosis, which results in progressive loss of kidney function, enhanced susceptibility to cardiovascular disease, and potentially end stage renal disease. CKD progression occurs even if the original cause of the kidney disease is no longer operant. Despite the worldwide prevalence of CKD, few therapeutic strategies have any impact on the prevention or treatment of fibrotic kidney disease.

One factor with a prominent role in fibrosis development in the kidney and other organs is TGF-β, which signals through the TGF-β–SMAD signaling pathway (2). TGF-β binds to cell surface type I and II serine/threonine receptor kinases, resulting in phosphorylation of SMAD2 and SMAD3, which are then released into the cytosol and bind in a complex with SMAD4. After translocation to the nucleus, the SMAD2/3/4 complex localizes to SMAD-binding elements within the genome to modulate expression of profibrotic and other target genes (Figure 1 and ref. 3). During kidney injury, a major source of TGF-β is proximal tubule epithelial cells, some of which are arrested in cell cycle phase G2/M (4). The release of TGF-β and other factors by the damaged epithelial cells and infiltrating inflammatory cells act in a paracrine fashion to activate interstitial fibroblasts/pericytes. Once activated, these interstitial cells convert to proliferative myofibroblasts and maladaptively deposit extracellular matrix, which leads to interstitial fibrosis (2, 5). Since TGF-β plays a major role in this pathophysiological response, there have been attempts to therapeutically interrupt the TGF-β signaling pathway with either small molecules or antibodies. Some of these approaches are currently in phase I and II clinical trials (6); however, there is still no accepted TGF-β-targeted therapy for kidney fibrosis.

**Conflict of interest:** The author or his family hold equity interests in Patientkeeper, AMAG, Pacific Biosciences, MediBeacon, Theravance, Sentiion, DnaNow, and DRP. Joseph V. Bonventre is a consultant for Janssen RND, Kyex, and editor of Seminars In Nephrology. Joseph V. Bonventre holds patents on KIM-1, which have been assigned to Partners Healthcare which has licensed them to Sekisui, Novaritis, Johnson and Johnson, BiogeniDke, and a number of research reagent providers. He has received research support from NovoNordisk.

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**Vitamin D signaling in the kidney**

Interaction of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] with the vitamin D receptor (VDR) modulates the transcription of more than 200 genes (7). The VDR forms a heterodimer with retinoid X receptors (RXRs) that together promote the recruitment of nuclear coactivators and the lysine acetyltransferase CBP/p300, which provides access for the basal transcriptional machinery through histone acetylation (Figure 1 and ref. 8). The VDR is expressed in more than 30 different tissues (9), including the kidney. VDR-