Researchers identify molecular predictor of metastatic prostate cancer

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Prostate tumors that carry a "signature" of four molecular markers have the potential to become dangerously metastatic if not treated aggressively, researchers at Dana-Farber Cancer Institute report in a study published online today by the journal *Nature*. The discovery lays the groundwork for the first gene-based test for determining whether a man's prostate cancer is likely to remain dormant within the prostate gland, or spread lethally to other parts of the body.

By analyzing prostate cancer tissue from hundreds of men participating in a national health study, dozens of whom died of the disease, investigators led by Ronald DePinho, MD, Lynda Chin, MD, and Zhihu Ding, PhD, of Dana-Farber, in collaboration with Massimo Loda, MD, of Dana-Farber and Brigham and Women's Hospital, and Lorelei Mucci, PhD, of Brigham and Women's and Harvard School of Public Health, found that the four-gene/protein signature more accurately predicted which patients would die from metastatic spread than did the conventional method. The standard measure of prostate cancer's aggressiveness, known as the Gleason score (which is based on cancer cells' appearance under a microscope), is accurate about 60 to 70 percent of the time depending on the skill of the pathologist. The four-gene signature method alone was accurate 83 percent of the time. Combining the markers and Gleason methods produced an accuracy of approximately 90 percent.

"It's widely recognized that many prostate cancer patients are treated unnecessarily," says DePinho, who is the director of Dana-Farber's

Belfer Institute for Applied Cancer Science. "The vast majority of prostate cancers would not become life-threatening, even if left untreated. But because we can't accurately forecast which are likely to spread and which aren't, there is a tendency to unnecessarily subject many men to draconian interventions."

The result, DePinho says, is that approximately 48 men are treated for prostate cancer for every life saved. The cost of such overtreatment is estimated at more than $600 million a year in the United States alone. There is a physical price as well. The main forms of prostate cancer treatment – surgery and radiation therapy – can produce a range of lasting complications, such as impotence and urinary problems, including incontinence.

The main obstacle to developing better prognostic tests for prostate cancer has been the lack of uniformity of cells in different tumors, and even within a single tumor. In 85 percent of prostate cancer cases, the prostate gland holds more than one tumor focus, each of which may contain a different assortment of cancer cells with a distinct set of gene abnormalities. Such diversity makes it difficult to identify genes or other features that reliably indicate a tumor's potential to spread.

In the current study, researchers began with the well-established fact that prostate cancers without a working copy of the Pten gene tend to remain fairly idle and don't trespass beyond the prostate gland itself. Researchers theorized that the loss of Pten in turn activates a collection of genes – a pathway – functioning to constrain the tumor's growth and invasion. If that pathway was shut down, they reasoned, the tumor would begin to break loose from the prostate and spread insidiously through the body.

Using computational biology techniques to analyze gene activity in mouse prostate cancer cells with inactive Pten, the investigators found a

few pathways that seemed to play a constraining role. One, known as TGF□-SMAD4 (for some of the genes that comprise it), was particularly intriguing as this pathway had been implicated in the metastasis of other tumor types in the past. When researchers conducted confirmatory molecular signaling studies to see what happens when Pten is knocked out of commission, signaling in the TGF□-SMAD4 pathway "shot through the roof," DePinho says, suggesting that the pathway had sprung into action.

When researchers generated mice whose prostate cells lacked both Pten and the Smad4 gene, the animals developed large, fast-growing tumors that spread to their lymph nodes and beyond. Guided by these insights, they then examined whether something similar was happening in human prostate cancers.

Comparing the gene expression profiles of indolent versus aggressive mouse prostate cancers, they found about 300 genes that distinguished the two groups. "We then categorized them for known functions," DePinho says. "We were encouraged to see that the top functional category were genes playing that have roles in cell division and movement" — actions that are needed for cancer cells to grow and spread with lethal consequences.

The researchers conducted an elaborate series of experiments to identify the genes most closely linked to the aggressive biology of prostate cancer. Among the hundreds of genes analyzed, two such genes stood out: SPP1 and CyclinD1, both of which, intriguingly, are close working partners of Smad4.

The four-gene signature – Pten, Smad4, SPP1, and CyclinD1 – showed its effectiveness as a predictive tool for survival when researchers drew on data from the Physicians' Health Study, which has been tracking the health of thousands of U.S. physicians for nearly 30 years. When the

investigators screened prostate cancer samples from study participants for the four-gene/protein signature, it was more accurate in predicting the ultimate course of the illness than conventional methods were.

"By integrating a variety of techniques – computational biology, genetically engineered model systems, molecular and cellular biology, and human tissue microarrays – we've identified a signature that has proven effective in distinguishing which men with prostate cancer are likely to progress and die from their disease and those who are not," DePinho remarks. "Efforts are already underway to use this knowledge to develop a clinical test – which we hope will occur within a year or so – that will enable doctors and patients to make more accurate treatment decisions and avoid unnecessary aggressive interventions which adversely impact on quality of life and deplete over-extended healthcare resources. This science holds potential to illuminate a long-sought answer for optimal management of this complex disease."

Provided by Dana-Farber Cancer Institute