New approach for late-stage prostate cancer

June 14 2013, by Bonnie Prescott

(Medical Xpress)—For the past 70 years, androgen deprivation therapy (ADT) has been the standard treatment for men diagnosed with late-stage prostate cancer.

By lowering the physiological production of testosterone, ADT deprives tumors of their "fuel" and slows prostate cancer growth. Although the hormone therapy is almost always effective in the short term, in a majority of patients tumors eventually grow resistant to ADT and cancer recurs.

Now, a study that uses a "co-clinical" approach to merge real-time data from genetically engineered mouse models with clinical data from patients who are studied in parallel, has identified several molecular pathways underlying ADT resistance. Led by a scientific team at Harvard Medical School and Beth Israel Deaconess Medical Center, the new findings offer potential for the development of tailored therapies for late-stage prostate cancer, while also confirming the value of the co-clinical research model to streamline and expedite biomedical investigations. The study currently appears online in *Nature Genetics*.

"Our findings represent a proof-of-principle of the validity of the co-clinical platform," explained senior author Pier Paolo Pandolfi, George C. Reisman Professor of Medicine at HMS and scientific director of the Cancer Center at Beth Israel Deaconess. "Prior to this, reactivation of the androgen receptor pathway was found to be a critical event responsible for resistance to ADT. Although this discovery led to the development of several new-generation ADT agents, these drugs only

partially overcame this resistance, highlighting the fact that other events must also be in play. Now we can see that the causes of androgen therapy resistance are dependent on a combination of diverse events that stem from the genetic complexity of prostate cancer."

By simultaneously analyzing mouse models of numerous genetic mutations and comparing the data from human tissue samples of ADT-resistant prostate cancer, the scientists were able to unravel key aspects of this complex genetic web. The team found that although ADT slows tumor growth in a Pten knockout mouse, when either Trp53 or Lrf are also absent, this response is blocked and ADT-resistant prostate cancer develops. The investigators additionally found that compound loss of Pten with Lrf or Trp53 triggers down-regulation of Xaf1 along with up-regulation of Srd5a1, indicating a treacherous new mechanism adopted by subtypes of prostate tumors to survive after testosterone withdrawal.

"By integrating these data from the various relevant mouse models and from patient samples, we have identified XAF1-XIAP/SRD5A1 as a predictive and, most important, actionable signature for late-stage prostate cancer that has grown resistant to ADT," explained Pandolfi, who originally conceived and developed the co-clinical trial method to help speed the clinical testing of targeted cancer therapies.

In this new study, a scientific team led by first author Andrea Lunardi, HMS instructor in medicine at Beth Israel Deaconess, set out to determine whether different combinations of some of the most frequent mutations reported to influence prostate cancer initiation and progression were also influencing tumor response to ADT. Employing the co-clinical research platform, the team compared data gathered from hundreds of mice replicating human cancer mutations with data gleaned from hundreds of patient samples.

The various "mouse proxies" were first subjected to ADT, and were then followed for several months. To determine the tumors' responses to ADT, the mice underwent monthly imaging by CT-PET scans, MRI scans or some combination of the two. Ultimately, these imaging data, together with pathologic, molecular and genetic analyses of the various mouse tumors, revealed a functional link between the genetic makeup of the tumors and the therapeutic responses. "This enabled us to define a new combination of molecular events engaged by the tumor to circumvent the ADT," explained Lunardi. "Our results showed that the combined inhibition of the XIAP, SRD5A1 and AR pathways overcame ADT resistance."

Continuing the co-clinical strategy, the investigators immediately translated this information to their cohort of prostate cancer patients. Their analyses revealed that the genetic and molecular data collected in the ADT-resistant mice robustly predicted the efficacy of the therapy in human patients, unraveling the same mechanisms of resistance in the poor responders as were observed in the mouse models. "This type of synchronized data collection provides a unique opportunity to help guide ongoing clinical trials with accuracy and precision," said Pandolfi. "These results were impressive, and most important, both of the mechanisms that were identified in this study are druggable."

As Pandolfi further noted, "As tumors with different genetic makeups can develop different forms of resistance to treatments, our strategy could be summarized as 'divide et impera', or divide and conquer. Translated into a therapeutic approach this essentially means, stratify the patients based on genetics and molecular criteria, and then decide on a combination of treatments."

Provided by Harvard Medical School