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Better understanding of bladder cancer subtypes might lead to improved treatments

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An international multidisciplinary team of researchers from a number of institutions, including Baylor College of Medicine, Brigham and Women's Hospital, the University of Texas MD Anderson Cancer Center, British Columbia Cancer Agency and the Broad Institute, who all are part of The Cancer Genome Atlas Research Network, has completed a comprehensive molecular characterization of 412 muscle-invasive bladder cancers that resulted in the identification of five cancer subtypes with different susceptibilities to specific therapies. The results, which appear in the journal *Cell*, might lead to future personalized therapies.

"Bladder cancer is not one but multiple diseases," said corresponding author Dr. Seth Paul Lerner, who is the director of urologic oncology and the Multidisciplinary Bladder Cancer Program, as well as professor of urology and Beth and Dave Swalm Chair in Urologic Oncology at Baylor. "Under the microscope, invasive bladder cancer from different patients may look very similar. We know there are many variations though that may affect response to treatment and long-term survival. This research provides a much broader and refined understanding of the molecular underpinnings associated with these variations".

In 2014, the researchers published in the journal *Nature* the results of a study of 131 bladder cancers that presented the first integrated multi-'omic' characterization of molecular alterations in this type of cancer, a major step toward personalized medicine and a hallmark of The Cancer Genome Atlas projects. The study presented here expanded the 2014 study with a much larger cohort, integrated more types of

genomic data and refined the molecular subtypes.

Understanding the molecular alterations and potential therapeutic targets for bladder cancer

"In this study, we tripled the number of bladder cancers studied, from 131 in 2014 to 412 in 2017, which resulted in the identification of 32 additional significantly mutated genes and added less common mutations that seem to be involved in this cancer," said Dr. John N. Weinstein, chair of bioinformatics and computational biology at the University of Texas MD Anderson Cancer Center. "These altered genes offer multiple opportunities for novel therapeutic interventions. Bladder cancer has one of the highest mutation rates, and it appears that the APOBEC signature mutagenesis is associated with this high mutation burden and is involved in up to 70 percent of the tumors. Tumors with the highest number of mutations and high APOBEC are associated with better survival than average."

In addition, integration of multiple molecular parameters, such as mutation, gene amplification, RNA and protein profiles, revealed that bladder cancer could be subdivided not into four subtypes, as the researchers had identified in 2014, but five subtypes. Each subtype, the researchers propose, may be associated with unique responses to therapies and this can be tested in future clinical trials.

"One prominent feature in this study is that we report survival analysis, which we did not report in the 2014 paper," said Lerner, who is also a member of the Dan L Duncan Comprehensive Cancer Center at Baylor. "Now, we are able to show that mutation signatures, molecular subtypes, load of new cancer-associated molecules, in addition to known clinical and pathological factors, have a very clear influence on overall patient survival."

The researchers propose that the information learned about bladder cancer should be taken into consideration when designing precision medicine clinical trials. This study and future research on the cancer subtypes might one day help physicians better match patients with specific, personalized therapies tuned to target the particular molecular signatures and other biological characteristics of their cancer.

"The project has produced a treasure trove of data – all of it now publicly available – that will be analyzed, interpreted and re-interpreted for literally decades by bladder cancer researchers to benefit bladder cancer patients and their families," Weinstein said.

"Bladder cancer causes an estimated 150,000 deaths worldwide per year, and we are behind other cancer fields in terms of the clinical applications of its molecular data and biology," Lerner said. "However, we can begin to see how we can use this information in the future to provide the best treatment for each patient."

More information: Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. *Cell*. DOI: dx.doi.org/10.1016/j.cell.2017.09.007

John N. Weinstein et al. Comprehensive molecular characterization of urothelial bladder carcinoma, *Nature* (2014). DOI: 10.1038/nature12965

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