Three differentiation states risk-stratify bladder cancer into distinct subtypes.

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Public Summary:
Current clinical judgment in bladder cancer (BC) relies primarily on pathological stage and grade. We investigated whether a molecular classification of tumor cell differentiation, based on a developmental biology approach, can provide additional prognostic information. Exploiting large preexisting gene-expression databases, we developed a biologically supervised computational model to predict markers that correspond with BC differentiation. To provide mechanistic insight, we assessed relative tumorigenicity and differentiation potential via xenotransplantation. We then correlated the prognostic utility of the identified markers to outcomes within gene expression and formalin-fixed paraffin-embedded (FFPE) tissue datasets. Our data indicate that BC can be subclassified into three subtypes, on the basis of their differentiation states: basal, intermediate, and differentiated, where only the most primitive tumor cell subpopulation within each subtype is capable of generating xenograft tumors and recapitulating downstream populations. We found that keratin 14 (KRT14) marks the most primitive differentiation state that precedes KRT5 and KRT20 expression. Furthermore, KRT14 expression is consistently associated with worse prognosis in both univariate and multivariate analyses. We identify here three distinct BC subtypes on the basis of their differentiation states, each harboring a unique tumor-initiating population.

Scientific Abstract:
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