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Genetic Alterations in the Molecular Subtypes of Bladder Cancer: Illustration in the Cancer Genome Atlas Dataset

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Abstract

Context: Recent whole genome mRNA expression profiling studies revealed that bladder cancers can be grouped into molecular subtypes, some of which share clinical properties and gene expression patterns with the intrinsic subtypes of breast cancer and the molecular subtypes found in other solid tumors. The molecular subtypes in other solid tumors are enriched with specific mutations and copy number aberrations that are thought to underlie their distinct progression patterns, and biological and clinical properties.
Objective: The availability of comprehensive genomic data from The Cancer Genome Atlas (TCGA) and other large projects made it possible to correlate the presence of DNA alterations with tumor molecular subtype membership. Our overall goal was to determine whether specific DNA mutations and/or copy number variations are enriched in specific molecular subtypes.
Evidence: We used the complete TCGA RNA-seq dataset and three different published classifiers developed by our groups to assign TCGA's bladder cancers to molecular subtypes, and examined the prevalence of the most common DNA alterations within them. We interpreted the results against the background of what was known from the published literature about the prevalence of these alterations in nonmuscle-invasive and muscle-invasive bladder cancers.
Evidence synthesis: The results confirmed that alterations involving *RB1* and *NFE2L2* were enriched in basal cancers, whereas alterations involving *FGFR3* and *KDM6A* were enriched in luminal tumors.
Conclusions: The results further reinforce the conclusion that the molecular subtypes of bladder cancer are distinct disease entities with specific genetic alterations.
Patient summary: Our observation showed that some of subtype-enriched mutations and copy number aberrations are clinically actionable, which has direct implications for the clinical management of patients with bladder cancer.

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1. Introduction

Recent whole genome mRNA expression profiling studies revealed that bladder cancers can be grouped into molecular subtypes, some of which share clinical properties and gene expression patterns with the intrinsic subtypes of breast cancer and the molecular subtypes found in other solid tumors. The molecular subtypes in other solid tumors are enriched with specific mutations and copy number aberrations (CNAs) that are thought to underlie their distinct progression patterns, and biological and clinical properties.

2. Evidence acquisition

We used the complete The Cancer Genome Atlas (TCGA) RNA-seq dataset and three different published classifiers developed by our groups to assign TCGA's bladder cancers to molecular subtypes, and examined the prevalence of the most common DNA alterations within them (Supplementary material). We interpreted the results against the background of what was known from the published literature about the prevalence of these alterations in nonmuscle-invasive and muscle-invasive bladder cancers.

3. Evidence synthesis

3.1. Clinical issues in bladder cancer

Clinical experience and emerging genomic data support the idea that bladder cancers progress along two largely nonoverlapping tracks (''papillary'' and ''nonpapillary'') that pose distinct challenges for clinical management [1–3]. Most nonmuscle-invasive bladder cancers (NMIBCs) belong to the papillary pathway and are characterized by the presence of activating type-3 receptor for fibroblast growth factor (*FGFR3*) mutations, downstream Ras pathway activation, wild-type *TP53*, and stable genomes [1–3]. Clinically, papillary NMIBCs are rarely lethal but recur almost always, necessitating that patients receive lifelong surveillance; the repeated surgical procedures required to deal with recurrences cause significant anxiety, discomfort, and morbidity, making bladder cancer the most expensive tumor on a per patient basis. A significant proportion of cases (15–20%) of NMIBCs progress to become muscle invasive [1,2]. However, currently no reliable tools are available to identify them before they become life threatening. The nonpapillary pathway is characterized by loss-of-function mutations and CNAs involving*TP53* and *RB1* and genomic instability [1,2]. It gives rise to aggressive, muscle-invasive bladder cancers (MIBCs), representing approximately 20–25% of all bladder cancers and causing death in approximately half of affected patients. Carcinoma in situ (CIS) is generally considered to be the precursor lesion for nonpapillary MIBCs [1,2], but comprehensive genomic data for CIS are not yet available, so this assumption awaits direct experimental validation. Patients with either high-grade papillary nonmuscle-invasive disease or CIS are currently treated with the same adjuvant therapy (intravesical Bacillus Calmette–Guerin [BCG] immunotherapy), but it is by no means clear that BCG produces comparable benefit in CIS and high-grade papillary tumors [1,2]. Many high-grade papillary tumors ultimately become BCG unresponsive, so clinicians are then faced with the dilemma of whether to continue using a bladder-sparing regimen or to employ definitive surgery. The latter is certainly too aggressive for those patients whose tumors could be controlled by local therapy, but again there are no reliable tools to distinguish the tumors that have the potential to metastasize from those that do not. Muscle-invasive disease is managed with definitive local therapy (chemoradiation) or surgery (cystectomy) with or without perioperative systemic cisplatin-based chemotherapy to treat subclinical metastatic disease, but it is still not possible to distinguish the patients who warrant chemotherapy from those who will not benefit from it. It would also be tremendously useful to have biomarkers that would enable patients and their physicians to choose between bladder-sparing regimens such as chemoradiation and cystectomy. Overall, it is hoped that by understanding the molecular mechanisms that give rise to papillary and nonpapillary bladder cancers, it will be possible to develop methods to inform clinical decision making at every step of disease progression and management.

3.2. Intrinsic subtypes of cancer

The widespread use of genomics to investigate cancer heterogeneity is transforming our understanding of cancer biology. A pioneering study in leukemia demonstrated that mRNA expression profiling could be used to distinguish ALL from AML with a high degree of accuracy [4], and a subsequent study used gene expression profiling to identify two previously unrecognized molecular subtypes of diffuse large B-cell lymphoma [5]. Importantly, patients whose tumors belonged to one of the subtypes (''germinal center-like DLBCL'') had better clinical outcomes than patients with the other (''activated B-like DLBCL'') [5]. Parallel studies in breast cancer revealed that they could also be grouped into ''intrinsic subtypes'' that had very different biological properties and behaved clinically as distinct disease entities [6,7]. Patients with basal-like or HER2-enriched breast tumors had poor clinical outcomes in the absence of systemic therapy, but many of them benefited greatly from neoadjuvant chemotherapy (NAC) [8,9]. Patients with HER2-enriched tumors also obtained significant clinical benefit from ERBB2 antagonists [10]. In the absence of perioperative chemotherapy, women with luminal tumors had better prognoses [11] and, when given perioperative chemotherapy, most patients also obtained little to no benefit [8,12]. Rather, they obtained major chemopreventive clinical benefit from adjuvant therapy with selective estrogen receptor modulators (SERMs), which reduced disease recurrence by about 50% [11]. In contrast, SERMs produced no benefit in patients with basal-like or HER2-enriched tumors [11]. Subsequent studies identified molecular subtypes in head and neck squamous cell carcinomas (SCCs) [13], glioblastomas [14], and pancreatic cancers [15],

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