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Review

Intrinsic subtypes and bladder cancer metastasis

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Abstract Recent studies demonstrated that bladder cancers can be grouped into basal and luminal molecular subtypes that possess distinct biological and clinical characteristics. Basal bladder cancers express biomarkers characteristic of cancer stem cells and epithelial-to-mesenchymal transition (EMT). Patients with basal cancers tend have more advanced stage and metastatic disease at presentation. In preclinical models basal human orthotopic xenografts are also more metastatic than luminal xenografts are, and they metastasize via an EMT-dependent mechanism. However, preclinical and clinical data suggest that basal cancers are also more sensitive to neoadjuvant cisplatin-based combination chemotherapy (NAC), such that most patients with basal cancers who are aggressively managed with NAC have excellent outcomes. Importantly, luminal bladder cancers can also progress to become invasive and metastatic, but they appear to do so via mechanisms that are much less dependent on EMT and may involve help from stromal cells, particularly cancer-associated fibroblasts (CAFs). Although patients with luminal cancers do not appear to derive much clinical benefit from NAC, the luminal tumors that are infiltrated with stromal cells appear to be sensitive to anti-PDL1 antibodies and possibly other immune checkpoint inhibitors. Therefore, neoadjuvant and/or adjuvant immunotherapy may be the most effective approach in treating patients with advanced or metastatic infiltrated luminal bladder cancers.

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1. Introduction

Urothelial bladder cancer is a highly heterogeneous disease with variable patterns of progression and responses to conventional and targeted agents [1]. Histopathologically, bladder cancers are grouped into two major subsets (papillary and non-papillary) that pose distinct challenges for clinical management [2]. Papillary bladder cancers rarely progress to become muscle-invasive and metastatic, but they are highly prone to recurrence, necessitating expensive life-long clinical surveillance with repeated surgical intervention [1,2]. Thus, a top research priority is to identify agents that produce long-term durable remissions in patients with this form of the disease. There is also a need to identify biomarkers that distinguish papillary cancers that pose no risk of progression to muscle invasion from the smaller fraction that do, so that more aggressive interventions can be applied early when the chance of cure is greatest.

On the other hand, non-papillary bladder cancers have a high risk of progression to muscle invasive and metastatic disease [1], and they therefore pose a major threat to the patient. It is believed that many of these cancers evolve from carcinoma in situ (CIS) [2], although many patients have advanced or metastatic disease at presentation. High risk papillary and non-papillary non-muscle invasive cancers are currently treated uniformly with intravesical bacillus Calmette-Guerin (BCG) [1], which is a tuberculosis-like mycobacterium that produces a local immune response that mediates tumor regression [3]. However, even though most (>70%) patients are initially rendered free of clinically detectable disease, most will also develop recurrences that can become BCG-unresponsive [4]. These tumors have a high risk of progression, and at this point clinicians are faced with the decision of whether to remove the bladder (cystectomy) or to make another attempt at bladder preservation with a different intravesical or systemic regimen. There are currently few viable candidates for the latter, but new immunotherapy approaches hold promise. For example, adenoviral interferon-alpha (Ad-IFNα) gene therapy produced durable clinical responses in over a third of patients with BCG-unresponsive disease in completed clinical trials [5], and a Phase III registration trial is now open that could lead to FDA approval. There are also open clinical trials examining the potential efficacy of immune checkpoint blockade in these patients [6].

Muscle-invasive bladder cancers are also clinically heterogeneous [1]. Approximately half of patients are cured by cystectomy with or without perioperative cisplatin-based combination chemotherapy, but the others experience very rapid disease progression to cisplatin-refractory and metastatic disease [1]. Bladder cancers tend to metastasize to the liver, lung, brain, and bone, but the molecular mechanisms underlying organ-specific metastasis have not been identified. Until very recently there were no effective treatment options for patients with advanced and/or metastatic disease, but exciting recent studies established that immunotherapy with blocking anti-PD1 or −PDL1 antibodies produces significant and durable benefit in about a quarter of these patients [7,8], which prompted the FDA to approve the anti-PDL1 antibody atezolizumab for advanced bladder cancer in May 2016.

Papillary and non-papillary bladder cancers appear to be caused by distinct genomic alterations [2]. Papillary cancers are characterized by very high frequencies (>70%) of activating mutations in the type 3 receptor for fibroblast growth factor receptor (FGFR3) [9]. The mutations cause constitutive ligand-independent dimerization of FGFR3, leading to downstream MAP kinase activation that drives proliferation. So far no mouse models of FGFR3-driven papillary bladder tumorigenesis have been developed, but expression of constitutively active mutant Hras under the control of a urothelium-specific (uroplakin) promoter causes papillary tumorigenesis [10], suggesting that FGFR3-induced Ras pathway activation probably plays a central role in transformation.

Non-papillary bladder cancers are more closely associated with inactivation of classical tumor suppressors, most notably *TP53* and *RB1* [2,9]. It appears that *TP53* mutations are present in precursor lesions (CIS) [2,9], but most of the published studies that support this conclusion used indirect methods to identify p53-mutant tumors (i.e., immunohistochemistry to detection high levels of p53 protein), so more direct methods, such as next generation DNA sequencing, will be required to confirm these results. Preclinical studies confirmed that *TP53* inactivation promotes the emergence of CIS and muscle-invasive tumors in mice exposed to the cigarette smoke nitrosamine carcinogen, BBN [11] and combined inactivation of *TP53* and *RB1* via expression of the SV40 large T antigen in the urothelium also drives CIS and non-papillary tumorigenesis in mice [12]. Inactivation of *TP53* and *PTEN* in the mouse urothelium produced similar effects [13].

Recent lineage tracing studies suggest that papillary and non-papillary bladder cancers also arise from different cells of origin [14,15]. The papillary non-muscle invasive tumors that arise spontaneously in BBN-treated mice originate via transformation of a cell within the intermediate and/or superficial (luminal) layer [14], whereas CIS and muscle-invasive tumors arise from Sonic hedgehog-expressing basal cell(s) [15]. It will be interesting to determine whether the genomic abnormalities that are observed in papillary and non-papillary cancers are only permissive for transformation in these more luminal or basal cells, respectively.

2. Intrinsic subtypes of bladder cancer

The introduction of whole genome technologies to catalog all of the mRNA expression patterns and DNA alterations in a given tumor has transformed our understanding of human cancers. The Cancer Genome Atlas (TCGA) and the International Cancer Genomics Consortium (ICGC) are examples of two high profile collaborative public projects that have exploited these capabilities to obtain comprehensive genomic portraits of dozens of human cancers, and parallel private efforts have further enhanced these efforts. One approach that has been used very successfully has been to use transcriptome profiling data to identify "molecular subtypes" of cancers that share gene expression signatures and by inference, biological properties. The highest profile early example of the successful utilization of this approach

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