Emerging Bladder Cancer Biomarkers and Targets of Therapy

George J. Netto, MD[a,b,c,*], Laura J. Tafe, MD[d,e]

KEYWORDS

• Urothelial carcinoma • Bladder cancer • Genomics • Targeted therapy • Clinical trials • Biomarkers

KEY POINTS

- Bladder cancer is a heterogeneous disease, and recent genomic studies have identified several potential therapeutic targets.
- Alterations in tyrosine kinase receptors, intracellular signaling pathways, such as the PI3K/AKT/mTOR pathway, cell-cycle regulators, chromatin remodeling, and immune mediation, are significant in disease progression, and therapies targeting many of these alterations are currently in clinical trials.
- Novel noninvasive strategies are being developed, using identification of genomic, epigenetic, and proteomic markers, for early detection and surveillance in urine and serum.

GENETIC AND MOLECULAR BIOMARKERS

Deciphering the molecular pathways of bladder cancer has accelerated the identification of prognostic and theranostic markers, allowed for the development of novel noninvasive early detection and surveillance strategies, and elucidated new targets of therapy in bladder cancer.[1–26] Although widespread clinical adoption of novel biomarkers has been limited due to lack of validation by multi-institutional randomized prospective trials, recent genomic studies[27–30] have spurred efforts to evaluate these therapies, and such trials are finally being launched.

GENOMICS OF BLADDER CANCER

Recent genomic studies have validated and expanded on previously identified genetic pathways of bladder cancer development and have unmasked additional crucial driver genetic alterations. Although earlier array-based gene expression studies highlighted differentially expressed genetic signatures capable of predicting recurrence and progression,[7–9,21,23,31–40] recent integrated genomic and protein analysis studies have better defined clinically relevant molecular subtypes of bladder cancer. By integrating genomic data from aCGH, gene expression arrays, targeted mutation sequencing analysis, and protein analyses, Lindgren and colleagues[29,38] brought to light 2 main genomic molecular circuits in urothelial carcinoma: the first characterized by *FGFR3* alterations, overexpression of *CCND1*, and deletions in 9q and *CDKN2A*; and the second by *E2F3* amplifications, *RB1* and *PTEN* deletions, gains of 5p, and overexpression of CDKN2A (p16). Alterations in *TP53*/MDM2 were

Disclosure Statement: The authors have nothing to disclose.

[a] Department of Pathology, The Johns Hopkins Medical Institutes, Baltimore, MD, USA; [b] Department of Oncology, The Johns Hopkins Medical Institutes, Baltimore, MD, USA; [c] Department of Urology, The Johns Hopkins Medical Institutes, Baltimore, MD, USA; [d] Department of Pathology, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, USA; [e] Geisel School of Medicine at Dartmouth, 1 Rope Ferry Rd, Hanover, NH 03755, USA

* Corresponding author. Department of Pathology, Johns Hopkins University School of Medicine, 401 North Broadway Weinberg 2242, Baltimore, MD 21231.

E-mail address: gnetto1@jhmi.edu

Urol Clin N Am 43 (2016) 63–76

http://dx.doi.org/10.1016/j.ucl.2015.08.006

0094-0143/16/$ – see front matter

demonstrated in advanced tumors in both groups. Lindgren and colleagues[29] first recognized the significantly worse prognosis associated with a gene expression profile of a keratinized/squamous phenotype; this molecular subtype was further validated by Choi and colleagues[27] (Fig. 1). Termed basallike and characterized by p63 activation, squamous differentiation, positive CK5/6, epidermal growth factor receptor (EGFR), and cluster of differentiation (CD)44 expression and lack of cytokeratin (CK)20, this subtype is clinically aggressive but potentially sensitive to neoadjuvant chemotherapy. Choi and colleagues[27] also characterized a luminal subtype typically enriched for activating *FGFR3* mutations, active estrogen receptor pathway, and ERBB2 and PPARγ expression profile, and a third subtype, characterized by wild-type TP53 gene expression and strongly associated with resistance to neoadjuvant methotrexate, vinblastine, adriamycin/doxorubicin, and cisplatin (MVAC) therapy. Interestingly, upon resistance to chemotherapy, tumors from the basallike and luminal subtypes also displayed the TP53 wild-type expression.[27]

Finally, The Cancer Genome Atlas (TCGA) project's comprehensive molecular characterization of bladder cancer[28] provided a genomic analysis of 131 high-grade muscle-invasive bladder cancers (MI-BC), which revealed a staggering 302

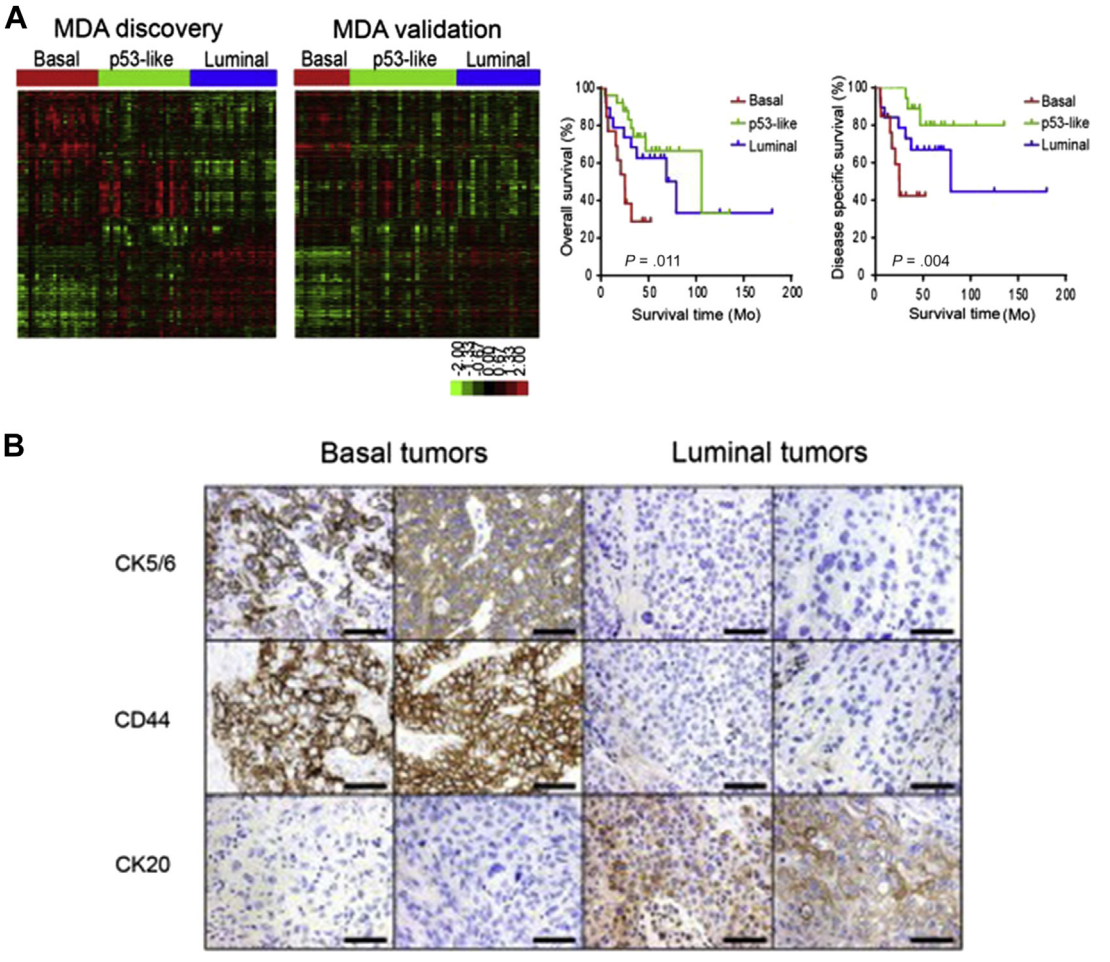

Fig. 1. (*A*) Three molecular subtype signatures (basal, luminal, and p53 wild-type signature) on whole genome mRNA expression (Illumina's DASL [cDNA-mediated Annealing, Selection, extension, and Ligation] platform). Corresponding Kaplan-Meier plots of overall survival and DSS are depicted. (*B*) Immunohistochemical analysis (CK5/6, CD44, and CK20) of basal and luminal marker expression. Representative basal (*left*) and luminal (*right*) tumors, as defined by gene expression profiling, are displayed. (*Adapted from* Choi W, Porten S, Kim S, et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell 2014;25(2):152–65; with permission.)