Molecular Biology of Bladder Cancer

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KEYWORDS

• Bladder cancer • Urothelial carcinoma • Mutations
• Somatic copy number alterations • Cell cycle • Epigenetics • Molecular subtypes

KEY POINTS

- There is a high rate of both mutations and genomic amplifications and deletions in muscle-invasive bladder cancer.
- *FGFR3* is commonly activated in bladder cancer, through either mutation, gene fusion events, or elevated expression, and is a potential therapeutic target.
- Chromatin regulatory gene mutations, Cell-cycle gene mutations, amplifications (cyclins), and deletions (cyclin-dependent kinase inhibitors) are very common in bladder cancer.
- Viral infection seems to contribute to bladder cancer development in 5% to 10% of cancers.
- The main RNA expression subtypes of bladder cancer are basal and luminal, similar to breast cancer, and confer both prognostic and therapeutic significance.
- The following genes and pathways are frequently affected: the ERBB family (including EGFR, ERBB2, and ERBB3), FGFR3, and the PI3K-mTOR (PI3KCA, PTEN, and TSC1) signaling cascade , many of which are potentially targetable using small molecule kinase inhibitors or antibody therapeutics.

BACKGROUND

Bladder cancer is a leading cause of morbidity and mortality, with nearly 400,000 new cases and 150,000 deaths worldwide.[1] However novel approaches to treatment in the past 2 decades have been sparse. Since 2006, of 126 approvals granted by the US Food and Drug Administration for hematology/oncology medications, none have been for the treatment of bladder cancer,[2] and chemotherapeutic approaches remain rooted in cisplatin-based combinations first introduced 30 years ago. This limited progress has provided major incentive to analyze molecular alterations in bladder cancer in detail in an effort to identify novel treatment approaches.

Bladder cancer genetics and molecular biology have historically provided important general insights into cancer biology, beginning with the discovery of *HRAS* as the first

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oncogene in a bladder cancer cell line.[3] Since that seminal discovery, multiple genes commonly subject to mutation in bladder cancer have been identified, including *TP53*,[4] *RB1*,[5] *TSC1*,[6] *FGFR3*,[7] and *PIK3CA*.[8,9] Furthermore, comparative genomic hybridization and related techniques were used extensively in bladder cancer, leading to identification of multiple amplified and deleted genes, including *PPARG*, *E2F3*, *EGFR*, *CCND1*, and *MDM2*, which are amplified, and *CDKN2A* and *RB1*, which are commonly deleted.[10–17] These and other molecular alterations involved in bladder cancer have been summarized in previous reviews.[16,18]

Recently, next-generation sequencing has enabled large-scale analyses, mainly focused on muscle-invasive bladder cancer, greatly expanding our understanding of this malignancy.[19–22] The initial next-generation sequencing studies were performed by the Beijing Genomics Institute,[20,21] in studies that focused initially on mutation identification,[20] and then included both mutation analysis and transcriptome studies.[21] More recently, The Cancer Genome Atlas (TCGA) project, funded by the National Cancer Institute, has performed a comprehensive analysis of 131 muscle-invasive bladder cancers, including assessment of mutations, copy number changes, expression profiling by RNA-Seq, micro RNA (miRNA) analysis, CpG methylation analysis, proteomic analysis of about 150 proteins, and integrated analyses of these data sets.

This review summarizes the current understanding of molecular alterations in bladder cancer, and focuses on findings from the TCGA project[19] and the Beijing group.[20,21] We also discuss recent reports providing improved understanding of molecular subtypes of bladder cancer based on expression analyses.

MOLECULAR ALTERATIONS IN BLADDER CANCER

Fig. 1 illustrates the major findings of the TCGA study, showing mutation rates and frequencies, gene deletions and amplifications, and changes in expression for genes of interest.[19]

Mutations in Bladder Cancer: General Findings

The TCGA study identified a relatively high rate of 7.68 mutations per Mb within coding regions, equivalent to 302 exonic mutations per cancer.[19] This mutation rate is exceeded among cancers studied in the TCGA project (now >20) only by lung adenocarcinoma, lung squamous cell carcinoma, and melanoma.[23] The mechanism or cause of this high mutation rate in bladder cancer is not known with certainty. Although smoking is associated with mutation rate and spectrum in lung cancer, this was not seen in bladder cancer,[19] despite the well-known epidemiologic association between cigarette smoking and bladder cancer. On the other hand, 51% of mutations seen in bladder cancer were TCW -> TTW or TGW changes ("TCW mutations" [C > T and C > G mutations] at T-C-A/T [TCW] trinucleotides), a class of mutation likely mediated by one of the DNA cytosine deaminases, in the APOBEC gene family.[24,25] In addition, APOBEC3B was expressed at high levels in all bladder cancers examined, suggesting a major role for APOBEC-mediated mutagenesis in the high mutation rate seen in bladder cancer.[19]

The Beijing group identified a somewhat lower overall mutation rate, but by statistical analyses identified significant levels of mutation in 37 genes. This included many genes identified previously, as well as multiple chromatin remodeling genes, namely, *KDM6A*, *ARID1A*, *CREBBP*, *EP300*, *KMT2A*, *NCOR1*, *CHD6*, and *KMT2C*.[20,21] In the TCGA analysis, 32 genes were identified as sustaining mutations at a significant rate (see **Fig. 1**B). There was considerable overlap between the genes