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Review Article

The evolution of bladder cancer genomics: What have we learned and how can we use it?

François Audenet, M.D., Kyrollis Attalla, M.D., John P. Sfakianos, M.D.*

Department of Urology, Icahn School of Medicine at Mount Sinai, New York, NY

Abstract

Background: With advancements in molecular biology techniques, great progress has been made in the understanding of urothelial carcinoma pathogenesis.

Objective: To examine the historic description of molecular alterations in bladder cancer and their evolution towards our current comprehension of the biology of the disease.

Results: Historically, a two-pathway model was described from histological and cytogenetic studies: low-grade papillary non-muscle invasive bladder cancers (NMIBC) were described to arise from epithelial hyperplasia with loss of chromosome 9 as an early event, whereas muscle-invasive bladder cancers (MIBC) were considered to develop from dysplasia, associated with genetic instability. Although there could be connections between the 2 pathways, NMIBC and MIBC were largely believed to develop secondary to different molecular alterations.

Next-generation sequencing has allowed important insights into cancer biology and a better understanding of the pathways involved in bladder cancer pathogenesis and heterogeneity. Urothelial carcinoma has been found to have a high frequency of somatic mutations compared to other solid tumors, including several mutations in multiple signaling pathways, such as cell cycle regulators (TP53, RB1), RTK/RAS/RAF pathway, PI3K/AKT/mTOR pathway and TERT gene promoter. Epigenetic changes and mutations in chromatin remodeling genes are especially frequent in bladder cancer. Mutations in FGFR3 and KDM6A are more common in NMIBC than in MIBC, whereas mutations in TP53 and KMT2D are more common in MIBC, suggesting the previously hypothesized 2 different pathways, with a subset of tumors progressing from NMIBC to MIBC.

Using comprehensive RNA expression profiling studies, at least 5 subtypes of bladder cancer have been identified, the most fundamental division being Basal/Squamous-like and Luminal. These subtypes have different prognoses, natural histories and responses to systemic treatments: Luminal subtypes are enriched with papillary histology and have a better prognosis, while Basal/Squamous-like subtypes are enriched with squamous features, are associated with advanced stage at presentation, and portend a worse prognosis.

Conclusion: This new understanding of bladder cancer will optimistically translate into better understanding of this heterogeneous disease and lead to improvement in patient outcome and quality of life through better tailored treatments.

Keywords: Urothelial carcinoma; Bladder cancer; Genetics; Pathways; Molecular subtypes

1. Introduction

Bladder cancer holds a significant burden to society, representing the ninth most common malignant disease and the thirteenth most common cause of cancer death worldwide [1]. In 2012, nearly 430,000 cases of bladder cancer were diagnosed worldwide and 165,000 deaths were recorded. According to the World Health Organization (WHO), the number of bladder cancer cases and deaths are expected to almost double in the near future [1].

Whereas systemic treatment has been limited to cisplatin-based chemotherapy with little progress over the past several decades, extensive analysis of molecular alterations in bladder cancer has now led to novel treatment approaches. Furthermore, a more accurate stage-specific classification could be helpful in better tailoring treatment based on the risk of recurrence and progression, and possibly on biomarkers [2]. These improvements require a detailed understanding of urothelial carcinoma pathogenesis

* Corresponding author. Tel.: +1-212-241-4812; fax: +1-212-987-4675.
E-mail address: john.sfakianos@mountsinai.org (J.P. Sfakianos).

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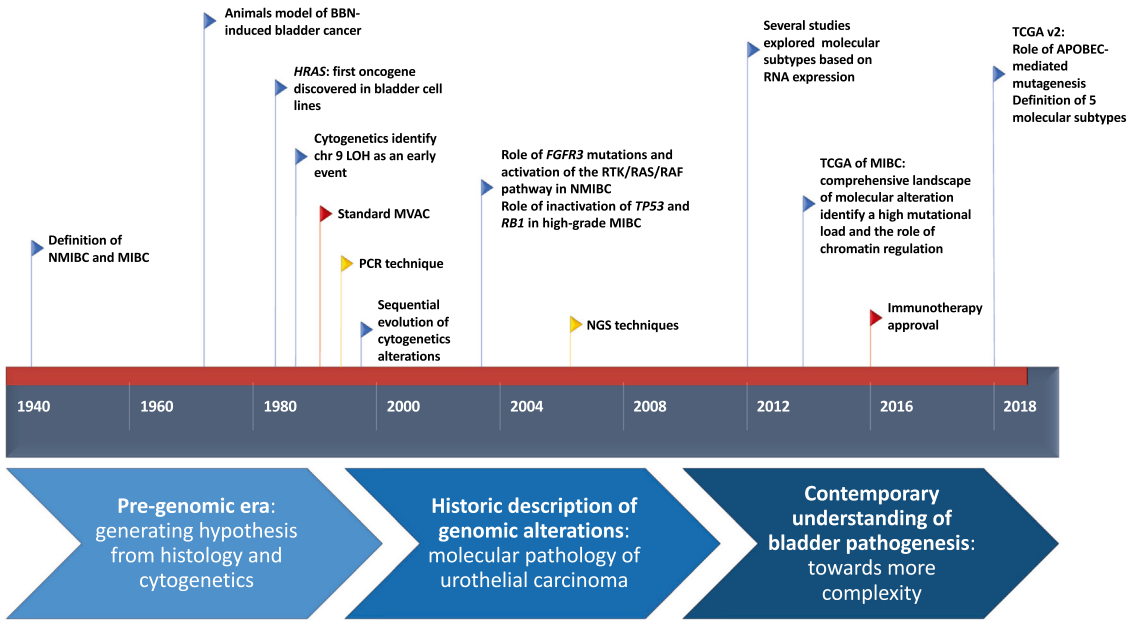

Fig. 1. Timeline of the discoveries in bladder pathogenesis. LOH = loss of heterozygosity; NGS = next-generation sequencing; PCR = polymerase chain reaction. (Color version of figure is available online.)

and molecular biology. Such an effort has been conducted over time, taking advantage of the progress and cost reduction in molecular biology techniques.

In this review, we examine the historic description of molecular alterations in bladder cancer and their evolution towards our current comprehension of the biology of the disease, thus leading to new molecular subtypes that may ultimately help improve patient care (Fig. 1).

2. The pregenomic era: Generating hypothesis from histology and cytogenetics

Before tools were available to explore molecular alterations, histology was the only way to evaluate and classify bladder tumors. This was based on the microscopic aspect and the depth of invasion within the bladder wall. Two clinically important presentations were defined: non–muscle-invasive bladder cancer (NMIBC), which is relatively benign but tends to recur, and muscle-invasive bladder cancer (MIBC), which has a propensity to metastasize [3]. The first experiments to explore the early steps of pathogenesis were conducted using animal models of BBN-induced bladder cancer [4]. In these studies, a temporal relationship was found to exist between epithelial hyperplasia (proliferation of normal cells), dysplasia (anomaly in growth and differentiation), carcinoma in situ (CIS), and invasive urothelial carcinoma. Furthermore, it appeared that CIS following epithelial hyperplasia was the earliest histologic malignant lesion and was observed to be irreversible, whereas hyperplasia could regress after withdrawing the carcinogen [4]. Based on these findings, 2 main pathways were hypothesized in the early 1980s in an effort to characterize the clinical course of bladder cancer [5]: low-grade papillary NMIBC was proposed to develop from hyperplasia without dysplasia, whereas dysplasia alone was hypothesized to lead to CIS, which could further progress to invasion of the lamina propria and muscle, with the possibility of lymphatic and hematogenous dissemination. Furthermore, high-grade papillary NMIBC was considered a result of the occurrence of hyperplasia and dysplasia combined, with a greater tendency to extend into lamina propria and beyond. These pathways were hypothesized to be interconnected. Besides this hypothetic sequence of progression, multifocal, independent tumors can also occur within the same patient due to the "field effect" of a globally altered urothelium [6]. However, the mechanisms necessary to initiate neoplastic transformation were unknown and no factor was identified to be predictive of the risk of recurrence or progression.

With the development of cytogenetics, it became possible to start investigating the molecular alterations of urothelial carcinoma. Several studies aimed to establish the relationship between cytogenetic aberrations and the multistep process of carcinogenesis [7]. Consistent with the 2 pathways theory, cytogenetic analysis of bladder tumors found that NMIBC had few cytogenetic changes (mainly loss of entire or portions of chromosome 9) and a stable karyotype, while MIBC exhibited genetic instability and had certain nonrandom cytogenetic changes (3p+, 3q+, 4p-, 5q-, 5p+, 6q-, 7p+, 10q-, -15, -18, 18p+, and -22) [7]. It was hypothesized that loss of chromosome 9 was associated with the transition of normal urothelium to hyperplasia and to low-grade papillary tumors [8], suggesting that loss of tumor suppressor genes on chromosome 9