Mini Review   **Open Access**

Urothelial Tumors: Moving from Morphology to Biology

Peter G Yousef and Manal Y Gabril[*]

Department of Pathology and Laboratory Medicine, London Health Sciences Centre, Western University, London, Canada

[*]**Corresponding author:** Manal Y Gabril, Department of Pathology and Laboratory Medicine, London Health Sciences Centre, Western University, London, Canada, E-mail: manal.gabril@lhsc.on.ca

Abstract

The fourth most common tumour of bladder is urothelial carcinoma. A great insight into the biology of the disease through molecular profiling and pathways analysis has been provided through the intense research involving the different molecular aspects of bladder cancer. Throughout this minireview, the general concepts of the molecular features of urothelial cancer will be reviewed. In addition, molecular-based classification for bladder carcinomas will be highlighted.

Keywords: Bladder carcinoma; Molecular classification

Review

Urothelial carcinoma constitutes more than 90% of bladder tumors which considered the second most common urologic malignancy. Based on the accumulated data of recent molecular studies, it is clear that the combination of molecular and pathological criteria can lead to better classification and consequently improves urothelial carcinoma management. Moving towards precision medicine, supplementing morphology with molecular analysis is clearly essential to be able to provide additional information to direct patient management [1,2].

Technological advances and the ability to perform high throughput analysis for gene, mutation, and epigenetic changes allowed us to move into a more in depth understanding of the pathogenesis of urothelial cancers. Recent studies have shown that molecular signatures can accurately classify urothelial carcinoma into two distinct groups regardless of morphology [3].

We believe that by classifying urothelial carcinoma into genetically distinct subgroups based on their genomic signatures could be helpful in understating the pathogenesis and inducing new therapeutic modules e.g. targeted therapy. The current clinical staging shows one substantial restraint in which the tumors of a similar stage and grade can have significantly different biology.

The molecular changes that occur in urothelial carcinoma are numerous and can be categorized into: (1) chromosomal alterations involved in early stages [4-7], (2) loss of cell cycle regulation accounting for cellular proliferation, and (3) metastasis, guided by events such as angiogenesis (Figure 1).

There is a difference in the molecular pathways between the noninvasive and invasive urothelial carcinomas. FGFR3, PI3K/AKT and RAS molecular cell cycle pathways are associated with non-invasive superficial urothelial carcinoma [8]. On the other hand, the pathways of cell cycle in invasive urothelial carcinoma include mainly tumor suppressor genes; TP3, p^{16} and RB. TP53 mutations induce a series of downstream effects, including decreased expression or loss of p^{21} (cell cycle arrest). LOH of the PTEN locus on chromosome 10 appears to be much more common in muscle invasive as compared with superficial tumors [7].

Hierarchical clustering studies have been classified high-grade stage T1 tumors into three distinct subgroups, with each having a unique copying number alteration, FGFR3, and p53 mutation status. Frequent FGFR3 mutation is detected in the first group. On the other hand, the third group did not have FGFR3 mutation, a strikingly low frequency of chromosome 9 loss but have prevalence of p53 mutant [7]. The second group had fewer chromosomal aberrations compared to the thirds. In addition, independent of tumor grade and stage, the status of p53 has been implicated as an important predictor of recurrence, progression and survival of patients with high grade recurrent superficial papillary urothelial carcinomas.
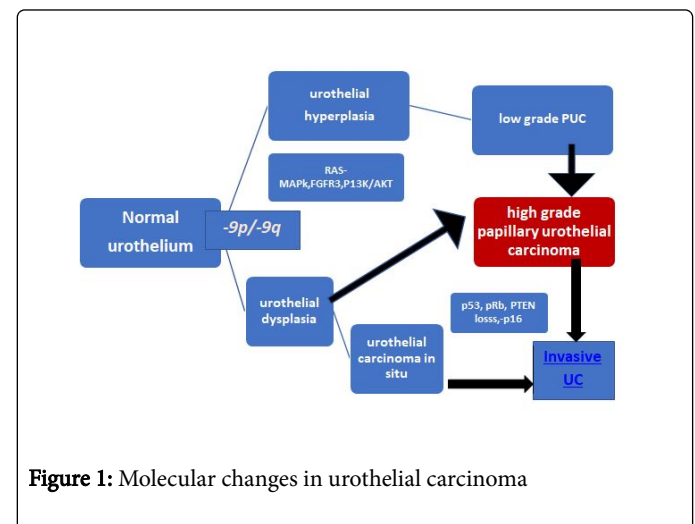

Figure 1: Molecular changes in urothelial carcinoma

Furthermore a recent study demonstrated that there is an infrequent number of FGFR3 mutations and chromosome 9 deletions and a distinct distribution of TP53 positivity according to grade/stage among young cases or early onset cases. These results suggest that early-onset tumors represent a differentially biologically driven entity [9].

Also, mutations of chromatin-structure regulating genes have been reported in urothelial cancer, as recently reviewed in details [10]. This includes mutations in SWI/SNF components, like ACTB. ARID1A, ATRID1B, ARID2, PBRM1, SMARCA4, SMARCC2 [10].

Papillary, low-grade, non-invasive constitutes the majority of urothelial tumors (70%) while only 20% of the cases are muscle-invasive disease (Stages pT2-pT4). Of special interest are the molecular changes in T1 high grade tumors (tumors invasive to the lamina propria only and represent 10%-20% of cases) which are challenging and complex. They have overlapping molecular features between the above two groups. A significant number of these pT1 tumors recur with muscle-invasive disease and require radical treatment. These tumors are thought to either grow de novo or evolve from high-grade carcinoma *in situ*.

Furthermore, stem cell-related genes can highlight subgroups of patients with non-invasive bladder cancers who are at risk of developing aggressive disease with shorter survival. Overexpression of embryonic stem-cell genes has also been reported in poorly differentiated high-grade urothelial carcinoma [11]. This could allow subclassifying urothelial carcinoma into more precise biological subgroups at the time of the diagnosis especially because urothelial carcinoma is known as a heterogeneous group of tumors. Heterogeneity of bladder cancer is challenging regarding management and prognosis [12]. A biological and molecular clarification of intratumoural heterogeneity of bladder urothelial carcinomas could be elucidated by cancer stem cells research [11].

It seems like in the near, rather than far, future incorporating biomarkers into nomograms/panel approach will be established in clinical practice to provide a reliable accuracy rate for prediction of advanced cancer stage, predicting disease recurrence after treatment, as well as predicting survival after treatment. It should be noted, however, that there is a still long way to go for translating research discoveries into the clinic [13].

The most important predictors for recurrence in non-muscle invasive disease are the prior recurrence rates, multiplicity and tumor size, whereas, significant predictors for progression include carcinoma *in situ* as well as tumor grade and stage. To predict outcome after radical cystectomy, the most common tool remains to be tumor, node, and metastases staging system, with lymph node involvement which in turn presents the most significant prognostic factor. Though, the predictive accuracy of staging and grading systems is limited. Although these parameters have provided useful estimates of survival outcome, large variation in outcomes within each stage and grade arises when considering the heterogeneity of tumor biology. Prediction of Patient outcomes can be improved by using different molecular markers, especially when incorporated in panels. Furthermore, these panels could have the potential to enhance the accuracy of predictive models and nomograms of urothelial carcinoma.

Molecular studies will help providing new diagnostic and prognostic biomarkers with the hope to advance the field of biomarker discovery and identify new effective targeted therapy. The detection of new molecular biomarkers is helpful in tumor diagnosis and monitoring recurrence and later for the identification of effective targeted therapy.

Also one of the studies mentioned that both markers cytokeratin and vimentin will be helpful markers in the early diagnosis of urothelial carcinoma. Wettstein et al. evaluated CD73 expression immunohistochemically in 174 patients with a primary urothelial carcinoma. They found that high CD73 expression was associated with favorable clinicopathological features such as lower stage, lower grade, less adjacent carcinoma *in situ*, and lower Ki-67 proliferation index as well as with better outcome [14].

Some biomarkers for non-invasive disease could improve the surveillance for tumor recurrence. Some of these biomarkers, such as UroVysion and ImmunoCyt/uCyt™ are FDA-approved for the detection of recurrent bladder cancer in voided urine specimens from patients with a history of bladder cancer [15,16]. There is significant published data showing that using combination of biomarkers (e.g. p53, RB and CDKs as p16 and p21) could enhance diagnostic performance, outcome prediction, and detection of recurrence of bladder cancer. Recently Circulating Tumor Cells (CTCs) detected in about 21% of the bladder cancer cases prior to cystectomy. It has been shown to be present in cases with metastatic urothelial carcinoma. Despite that the CTC detection can contribute to tumor diagnosis and identify patients with metastatic bladder cancer, such assays cannot be used as initial screening diagnostic tests due to their low sensitivity [17].

For therapeutic intervention and the prediction of patients respond to systemic treatment, molecular advances can also identify targets. However, currently, unsatisfactory results for urothelial cancers have emerged from various clinical trials of targeted agents. In addition, for targeting advanced urothelial carcinoma, neither monotherapy or in combination with cytotoxic chemotherapy have been approved as biologic agents. We believe that, in the near future; personalized/targeted therapy will substitute traditional surgical management of urothelial carcinoma. Also, we predict that a vaccine against urothelial carcinoma could take place in the near future or eventually.

References

1. Diamandis M, White NM, Yousef GM (2010) Personalized medicine: marking a new epoch in cancer patient management. Mol Cancer Res 8: 1175-1187.

2. Di Meo A, Pasic MD, Yousef GM (2016) Proteomics and peptidomics: moving toward precision medicine in urological malignancies. Oncotarget 7: 52460-52474.

3. Wu XR (2005) Urothelial tumorigenesis: a tale of divergent pathways. Nat Rev Cancer 5: 713-725.

4. Hurst CD, Platt FM, Taylor CF, Knowles MA (2012) Novel tumor subgroups of urothelial carcinoma of the bladder defined by integrated genomic analysis. Clin Cancer Res 18: 5865-5877.

5. Singh A, Settleman J (2010) EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer. Oncogene 29: 741-751.

6. Arndt H, Gudrun S, Dirk Z, Edwin H, Alfons H, et al. (2002) Occurrence of chromosome 9 and p53 alterations in multifocal dysplasia and carcinoma in situ of human urinary bladder. Cancer Res 62: 809-818.

7. McConkey DJ, Lee S, Choi W, Tran M, Majewski T, et al. (2010) Molecular genetics of bladder cancer: Emerging mechanisms of tumor initiation and progression. Urol Oncol 28: 429-440.

8. Kompier LC, Lurkin I, van der Aa MN, van Rhijn BW, van der Kwast TH, et al. (2010) FGFR3, HRAS, KRAS, NRAS and PIK3CA mutations in bladder cancer and their potential as biomarkers for surveillance and therapy. PLoS One 5: e13821.

9. Weyerer V, Schneckenpointner R, Filbeck T, Burger M, Hofstaedter F, et al. (2017) Immunohistochemical and molecular characterizations in urothelial carcinoma of bladder in patients less than 45 years. J Cancer 8: 323-332.

10. Chen J, Herlong FH, Stroehlein JR, Mishra L (2016) Mutations of Chromatin Structure Regulating Genes in Human Malignancies. Curr Protein Pept Sci 17: 411-437.

11. Ben-Porath I, Thomson MW, Carey VJ, Ge R, Bell GW, et al. (2008) An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors. Nat Genet 40: 499-507.

12. Hafner C, Knuechel R, Stoehr R, Hartmann A (2002) Clonality of multifocal urothelial carcinomas: 10 years of molecular genetic studies. Int J Cancer 101: 1-6.

13. Ibrahim R, Pasic M, Yousef GM (2016) Omics for personalized medicine: defining the current we swim in. Expert Rev Mol Diagn 16: 719-722.

14. Marian SW, Lorenz B, Thomas H, Filip R, Daniel E, et al. (2015) CD73 Predicts Favorable Prognosis in Patients with Nonmuscle-Invasive Urothelial Bladder Cancer. Dis Markers 15: 785461.

15. Mian C, Maier K, Comploj E, Lodde M, Berner L, et al. (2006) uCyt+/ImmunoCyt in the detection of recurrent urothelial carcinoma: an update on 1991 analyses. Cancer 108: 60-65.

16. Mian C, Lodde M, Comploj E, Palermo S, Mian M, et al. (2005) The value of the ImmunoCyt/uCyt+ test in the detection and follow-up of carcinoma in situ of the urinary bladder. Anticancer Res 25: 3641-3644.

17. Knowles MA, Aveyard JS, Taylor CF, Harnden P, Bass S (2005) Mutation analysis of the 8p candidate tumour suppressor genes DBC2 (RHOBTB2) and LZTS1 in bladder cancer. Cancer Lett 225: 121-130.