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Seminars Article

Editorial: Bladder cancer within the focus of basic and clinical research. Sixth IBCN Seminars Series

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Based on the presentations and discussions at the 15th meeting of the International Bladder Cancer Network (IBCN) in Lisbon, Portugal, the board of the IBCN assigned three of the selected presentations to this IBCN Seminar Series 2018, Part I. The included manuscripts cover translational topics investigating the origin and evolution of bladder cancer, as well as postoperative follow-up and quality of life after cystectomy.

1. On the tracks of the origin of bladder cancer

Smoking exposure is one of the most important risk factors for the development of bladder cancer. This relationship was used by researchers for the chemotoxic induction of bladder cancer in rodents [1,2]. These cancers have specific molecular phenotypes. *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN)-induced tumors become rapidly invasive and most often have a basal/squamous cell carcinoma like molecular subtype [1]. In contrast, *N*-methyl-nitrosurea-induced tumors arise as papillary lesions, may become invasive in the later follow-up and have a urobasal molecular subtype [2]. Fantini et al. aimed to compare the subtypes seen in these mouse models with gene expression signatures seen in the tumors of smokers with the anticipation that such comparisons may shed light into the development of bladder cancer [3].

The authors investigated the molecular landscape of muscle-invasive bladder cancers from The Cancer Genome Atlas dataset between smokers and nonsmokers. These findings were compared with their previous work on characterizing the molecular landscape of BBN-induced bladder cancers in mice [1]. The group found similarities of bladder cancers from smokers and BBN-induced bladder cancers in mice. Interestingly, the genomic similarities were more striking than transcriptomic similarities. However, differences of the molecular landscape of bladder cancers between smokers and nonsmokers were not as prominent as one would expect, especially when considering known differences in lung cancer. While it seems to be proven that smoking exposure is associated with a higher risk of bladder cancer, the mechanism by which it induces bladder cancer remains unsolved. Several thousand metabolites from smoking are excreted in a patient's urine, which may prevent the direct identification of molecular alterations due to smoking exposure. The cancer predisposition in the bladder of smokers may be better deciphered in the morphologically normal appearing bladder than in already established muscle-invasive bladder tumors. Molecular mechanisms of the evolution of bladder cancer are still not fully understood. However, such an understanding will be mandatory for the identification of novel targets that can be exploited to prevent the development of bladder cancer.

This is the introduction to the IBCN Seminar guest edited by Dr. Bernd Schmitz-Drager and supervised by Dr. Droller.
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2. What depth of resolution is needed to reveal molecular heterogeneity of bladder cancer?

Several facets indicate the high degree of heterogeneity of bladder cancer. The clinical course of patients varies dramatically, 13 morphologic variants have been described [4] and several groups have identified significant molecular heterogeneity between bladder cancers [5-7].

As bladder cancer datasets on the genomic and transcriptomic landscape have grown, the heterogeneity has become even more apparent. This is exemplified by the evolution of molecular subtyping of bladder cancer, which has become more granular over time. The simplest system distinguished 2 groups, basal- and luminal-like, but others included 3 to 5 groups, and the most recent system included even 10 distinct molecular subtypes [7]. The most recent identified subtype, neuroendocrine-like, could only be detected due to an increase of sample size. To what depth of resolution do we need to go for a complete understanding of the biology?

Warrick et al. investigated the molecular phenotype of different morphological variants [8]. Not surprisingly, the phenotypes were different between variants and, for example, the squamous variant most frequently showed a basal-squamous subtype. Similar to this work, a manuscript in the current issue of *Urologic Oncology* by Genitsch et al. compared molecular characteristics of urothelial carcinoma and the sarcomatoid variant in the same tumor [9]. Both components most often showed a basal-like subtype while the sarcomatoid variant was enriched for epithelial-to-mesenchymal transition.

The next level to defining "*true*" intratumor heterogeneity, including differences between cancer cells and the tumor microenvironment, may be single-cell analysis. Kiss et al. revealed a new dimension of resolution of tumor heterogeneity by single-cell profiling of bladder cancers [10]. They determined single-cell mRNA sequencing and identified different cell-subpopulations within the same tumor, including epithelial, mesenchymal, and immune lineages. Other techniques such as cytometry by time-of-flight mass spectrometry or co-detection by indexing measure protein abundance on the surface or within cells and allow a detection of up to approx. 60 targets at the same time. This spatial resolution within the tumor may reveal new insights that have not been apparent by performing sequencing of bulk tumor. Ideally this information will be linked with functional investigations and/or with robust clinical information to make it more applicable to our understanding of tumor biology. Otherwise these data will simply be snapshots of tumor biology at a higher granularity.

3. Can we predict the clinical course of patients undergoing cystectomy and can addressing risk factors prior to surgery impact length of hospital stay?

Assessing the clinical course of our patients with bladder cancer is of utmost importance in optimizing patient management. At the first visit in the outpatient clinic, the patient needs to gather extensive information about the future treatment course and recovery phase. Therefore, not only surgical options and systemic treatments but also the clinical course, length of hospital stay and quality of life, for example, 1 year after surgery are of interest to the patient. Models predicting such outcomes can serve as a foundation to counsel patients during pretreatment consultations.

Ray-Zack et al. discovered and validated a model for predicting the length of hospital stay in patients undergoing radical cystectomy [11]. This model allowed the authors to identify patients at-risk for prolonged hospital stay. Of course, policies guiding patient discharge differ widely between hospitals and regions, and particularly between Northern America and Europe. While these policies will affect the absolute length of hospital stay, parameters that put patients at-risk for a prolonged hospital stay (most likely due to peri- or postoperative complications) will be comparable between different continents. Therefore, these data might help us provide more information to the patient pre-operatively, identify patients at-risk for delayed discharge, and address the likely causes of delayed discharge even before surgery.

Conflict of interest

None.

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