EBioMedicine 30 (2018) 5–6

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Large-Scale Urinary Proteome Dataset Across Tumor Types Reveals Candidate Biomarkers for Lung Cancer

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Early detection of cancer remains one of the current main challenges. To date, lung cancer diagnosis is based on invasive tissue biopsies. To improve the detection of lung cancer, non-invasive biomarkers are needed. Urine is a very attractive non-invasive source for biomarkers that can signify disease. Moreover, compared to blood, urine is a less complex biofluid for biomarker discovery methods such as LC-MS/MS based proteomics. Due to the close proximity, urine has been widely studied as a biomarker source for urogenital biomarkers, including that of kidney, bladder and prostatic diseases. Urine contains a mixture of soluble proteins and extracellular vesicles (EVs) that harbour both RNA and proteins. Several urinary EV proteins have been related to the presence of prostate cancer cells (Duijvesz et al., 2015; Bijnsdorp et al., 2013). Even though urine is less complex than blood, it may still contain proteins other than from proximal organs (Melkonyan et al., 2008). For example recent studies showed the potential of urine (EVs) for detection of disease in more distant organs like the lungs and breast (Li et al., 2017; Liu and Liu, 2018).

In *EBioMedicine*, Zhang et al. have performed large-scale label-free urine proteomics of in total 231 patients in a case-control set-up to enable biomarker discovery for lung cancer diagnosis (Zhang et al., n.d.). The discovery set consisted of healthy age and gender-matched controls ($n = 23$) and lung cancer patients ($n = 23$). Using random forest analysis the authors identified a panel of 5 proteins that are specifically related to lung cancer, including Ferritin light chain (FLT), Mitogen-Activated Protein Kinase 1 Interacting Protein 1 Like (MAPK1IP1L), Fibrinogen Beta Chain (FGB), Member RAS Oncogene Family (RAB33B: RAB33B and RAB15: RAB15) (Zhang et al., n.d.). The identified 5-protein panel was not deregulated in urine samples from benign pulmonary conditions and five other cancers ($n = 14$–47 per set). Therefore these 5 proteins may serve specifically as non-invasive biomarker-panel to indicate whether lung cancer is present.

The above results are relevant for several reasons: 1. This is the first large-scale urine proteomics study including multiple disease types. 2. It further emphasizes the potential of urine for non-invasive cancer detection in a distant organ (lung cancer). 3. The data are available on-line and therefore could be mined to identify additional cancer/disease specific urinary protein profiles within the different patient groups that were measured. Such analyses will allow to explore the use of urine as protein biomarker source to identify cancer at an early stage.

Urine biomarkers are frequently found within EVs. The authors performed the analyses on an ultracentrifugation pellet of urine. Based on the identified proteins and candidate biomarkers (several RAB proteins), it seems that the samples were enriched for EVs. While EVs were previously thought to be a mechanism for discarding degraded cellular components, increasing evidence demonstrates that EVs are important mediators in intercellular communication (Maas et al., 2017). However, the isolation of extracellular vesicles from urine remains a challenge and ultracentrifugation is not compatible with routine testing in clinical practice. Ideally, urine is precleared from cells and debris by differential centrifugation before EV isolation. Currently, there are only few clinical applicable methods described that isolate EVs that are similar to those isolated by gold-standard ultracentrifugation (Bijnsdorp et al., 2017). To determine the significance of the findings for lung cancer non-invasive diagnosis, the validation of the identified proteins in independent patient cohorts will be an important step towards the clinical implementation of a urine biomarker test. Whether this test will be mass spectrometry-based or antibody-based remains to be determined. Hospitals that store urine samples in their biobank with the same protocol is another important requirement. Therefore, urine collection, processing and biobanking protocols need to be harmonized between different laboratories and hospitals. A small change in protocol can, lead to major differences in the identified profiles. The collection protocols were not specified by Zhang et al. (n.d.), therefore the differences in the profiles between different patient groups that were identified may also be a result of different storage procedures.

Measurement of urine or urinary EV protein profiles will be a promising diagnostic tool for the identification of cancer. Future studies with a large number of patients are needed, comparing the profiles of large patient groups with different diseases and disease stages. Then, we will find out that protein profiles within urinary EVs will be a game-changer in the early detection and as non-invasive test to identify cancer.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.03.009.
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https://doi.org/10.1016/j.ebiom.2018.03.012

Disclosure

The authors declared no conflicts of interest.

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