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Editorial

Prostate Cancer Biomarkers: Highly Specific, But What Does it Mean?

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EDITORIAL

In prostate cancer, the expression pattern of biological markers characteristic for tissue and stage-dependent molecular events is basically well-known and often applied in clinical settings as well as in molecular studies. Prostate-specific antigen (PSA), particularly, is defined as a biomarker for the diagnosis, monitoring, and risk prediction of prostate cancer, however, its use is limited and consequently has been discussed controversially [1]. PSA protein is produced in the epithelium of the prostate and therefore may be liberated into the blood stream after an epithelial disruption independently from malignant progression. Thus, PSA is not specific for prostate cancer. Since PSA expression has been found modulated in prostate cancer tissue and prostate cancer cells, however, PSA protein levels may reflect, in the main, differences in prostate cancer progress.

Beyond PSA, androgen receptor (AR), prostatic acid phosphatase (ACPP), prostate-specific membrane antigen (PSMA), and fatty acid synthase (FASN) are directly involved in prostate physiology and, therefore, are commonly accepted and widely used as prostate cancer correlated biomarkers for a long-time [2-5]. In terms of molecular studies cytokeratin 5 (CK5), cytokeratin 8 (CK8), and cytokeratin 19 (CK19) have been confirmed to be reliable markers of malignant cells [6-8]. Furthermore, the cell surface proteins E-cadherin (CDH1) and epithelial cell adhesion molecule (EpCam) were applied to verify the epithelial origin of cancer cells [9,10], often confirmed by counterstaining of the fibroblast-specific protein 1 (FSP1) which is specific for mesenchymal cells [11].

One important prerequisite for the use of biomarkers in clinical practice as well as in molecular research is the preparation and the detection of the molecules. Here, polymerase chain reaction (PCR)-based technologies are valuable and frequently established in urological laboratories. In general, PCR is a highly acknowledged method of choice; however, nucleic acid degradation by cellular and environmental RNases may prevent the precise quantification of biomarkers on the level of mRNA. Alternatively, enzyme-linked immunosorbent assay (ELISA) is routinely performed as part of the biomaker assessment. Here too, the quality of storage and preparation of samples primarily determine the quality of the biomarker measurement. From this, it follows that the methodology of biomarker analysis should be taken into consideration when evaluate the validity of a biomarker assay. Moreover, although the levels of mRNA and proteins are frequently correlated during gene expression, this might not always be the case, and transfer of biomarkers validated at the mRNA level to protein and vice versa has to be done carefully.

Moreover, the variability of biomarker expression has to take into account. Beside individual differences between patients, and thus also between patient samples, there are also differences regarding the molecular subtypes of prostate cancer. And finally, and most important, there is a pathological shift of the biomarker pattern during cancer progression including anticancer treatment. Temporal changes in the pattern lead to the distinct expression of early-stage and late-stage biomarkers. Additionally, the microenvironment appears important in cancer cell specification. Thus, in case of experimental approaches, prostate cancer cells may lose their specific biomarker pattern due to a loss of environmental signals in ex vivo approaches, e. g. primary cell culture and tissue models.

There are several studies affirming highly variable expression rates of the generally accepted biomarkers in prostate cancer diagnosis and research [12-15], suggesting, that some of them fail to be specific enough. Particularly old-established biomarkers, which were defined a long time ago, may be limited in validity and should be re-evaluated by performing recent detection techniques. Finally, there is still a need for further appropriate biomarkers, e.g. microRNAs, to improve the panel of prostate cancer-specific factors.

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