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Exosomal microRNAs as potential biomarkers in Castration Resistant Prostate Cancer.

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Castration-resistant prostate cancer (CRPC) develops as metastatic prostate cancer patients inevitably progress and become resistant to treatment targeting the androgen signalling axis; it represents the final stage of the disease with a median survival of less than two years. Although CRPC remains incurable, a number of treatment alternatives that gives modest prolongation of life have been developed and FDA approved during the last few years, *e.g.* selective adrenal inhibitors, androgen receptor signalling inhibitors, novel immune compounds, and less toxic radio nucleotides. The progression towards more personalised treatment strategies is however hampered by the lack of easily implemented reliable biomarkers predicting response to therapy and survival. In this month's issue of *European Urology*, Huang et al., attempts to address this issue [1]. They have investigated the prognostic potential of microRNAs (miRNAs) within exosomes in circulation and propose that two miRNAs, miR-375 and miR-1290, can serve as a prognostic biomarker in CRPC.

The miRNAs identified here are derived from exosomes in the blood circulation; extensive attention is now being paid to these vesicles as a source of biomarkers as their content resembles that of the cell of origin. In 2008, Skog *et al*. showed the miRNA content of extracellular vesicles to be reflective of the miRNA expression profile of the cells they originate from [5], however, it should be noted that the miRNA content of the exosomes is not an uncorrupted sampling of the contents in the parental cells. When investigating the content of the plasma derived exosomes (or extracellular vesicle) Huang *et al*. found mature miRNAs to be the most common RNA species [1]. This is in agreement with earlier sequencing of the RNA content in prostatic tissues that also identified miRNA as the most abundant class, constituting 95% of the RNA pool [2]. The miRNAs are not only the most abundant, but also technically suitable as biomarkers, as they can be easily and sensitively detected in small samples sizes by qRT-PCR and are stable in serum and plasma and resistant to extended storage, freeze-thawing and extreme pH [3]. Over the last decade, miRNAs have been found to be deregulated in prostate cancer and emerged as key players in cancer

progression and many studies highlight their diagnostic and prognostic potential [4]. Nevertheless, the current study does not confirm that it is the expression of the individual miRNAs that are changed; it could also be the exosomal content in circulation or the RNA content of the exosomes. As this also would be of great interest, it would have been informative to combine the evaluation of individual miRNAs with an evaluation of the amount of extracellular vesicles and their RNA content. The choice of reference genes is as important as the target genes in these studies, in the discussed study 192 plasma samples are investigated to identify the endogenous reference control including men, women, healthy and other types of cancer as well as 23 cases in the screening cohort. One of the reference genes, miR-30e, have been reported to be highly expressed in blood cells, particularly in monocytes [6] this could indicate that a difference in exosomal content is emphasised.

The first report of miRNAs as potential non-invasive diagnostic markers in a prostate cancer setting came in 2008. Mitchell *et al.* compared a panel of miRNAs in serum from healthy men to men with advanced prostate cancer and found that miR-141 was elevated in the cancer samples [7]. Giving the heterogeneity of prostate cancer it is not surprising that although many miRNAs have since been implicated as diagnostic and prognostic makers, no single miRNA has been consistently validated or implemented as a biomarker in clinical management of prostate cancer. In line with this, Huang *et al.* show that the combination of miR-375 and miR-1290 gives increased significance in prediction of survival compared to individually. The patients with high levels of both miR-375 and miR-1290 have significantly higher mortality rate than the patients with low levels of the two miRNAs at the 20 month follow up. There is also a significant difference in the median overall survival of patients with high levels of miR-375/1290 compared to the patients with low levels. Incorporation of miR-1290/-375 into a clinical prognostic factors-based model based on PSA and ADT failure time, also significantly improved the predictive performance. It would have been very

interesting to have a comparison to CellSearch for the exosomal miRNAs as CellSearch is currently the only FDA approved prognostic biomarker for CRPC. If would also make it easier to compare with other similar studies *e.g.* a recent study by Danila *al*. that found a 5-gene panel measured in blood samples from 97 metastatic CRPC patients to be prognostic predictor for survival, comparable with the CellSearch system. Further, if combining the gene panel and CellSearch the prognostic powers were enhanced compared to CellSearch alone [8].

It is evident that CRPC is a heterogeneous disease and given the complexity of the AR signalling cascade, the idea of a more complex panel of marker is appealing. Investigation if the inclusion of several miRNAs would give more representative information on the patient status and how much this could be improved is possible in the Huang *et al.* data set as the data of 375 known miRNAs and 57 putative miRNAs is available. For example, one of the predicted miRNAs on chromosome 12 seems to have excellent potential. It is however encouraging that one of the miRNAs identified in this paper, miR-375, has been described previously in several independent studies to be elevated in metastatic CRPC serum as the authors discusses. Two cohorts are used in this study, a screening cohort of 23 individuals and a validation cohort constituting 100 men. Hopefully, there will be future validation of presented biomarkers in larger independent cohorts to establish their reliability and potential clinical applicability. To conclude, the current paper by Huang *et al*. reinforce the notion that novel non-invasive prognostic methods for patients with CRPC will soon be a reality.

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Conflict of interest: The authors have nothing to disclose.