ID: 01015
Type: Poster
Topic: Liquid biopsy and biomarkers

Identification and validation of miRNAs with predictive and prognostic values for bladder cancer on liquid biopsy.

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Introduction: Bladder cancer (BC) represents a clinical and social challenge due to its high incidence and recurrence rates, as well as the limited advances in effective disease management. Currently, a combination of cytology and cystoscopy is the routinely used methodology for diagnosis, prognosis and disease surveillance. However, both the poor sensitivity of cytology tests as well as the high invasiveness and big variation in tumor stage and grade interpretation using cystoscopy, emphasizes the urgent need for improvements in BC clinical guidance. Accordingly, liquid biopsy represents a new non-invasive approach to diagnosis and follow-up of BC patients, becoming a promising strategy. Therefore, finding appropriate urine biomarkers capable of distinguishing between BC patients and healthy controls, as well as patients suffering other urogenital pathologies, is essential for patients. This approach would allow improving the predictive values of recent gold standard methods and life’s quality of patients during surveillance and decreasing the high cost for the National Health systems that this disease involves. In this context, microRNAs have demonstrated to be potential biomarkers, presenting very homogeneous expression among individuals and a high stability in liquid biopsy samples, such as urine.

Objectives: The main aim of this work is to find microRNAs in tissue and liquid biopsy samples with good predictive capabilities to diagnose BC patients.

Methods: Normal and tumor tissue samples as well as urine samples were collected from patients and healthy donors at the Urology Department of the University Hospital “12 de Octubre”. Informed consent was obtained from all patients. To determine differentially expressed miRNAs between normal and tumor tissues in bladder, total RNA was isolated and a LIMMA analysis was performed to data obtained from Affymetrix HuGene-1_0-st-v1 platform. To validate these results in tumor tissue and patient urine samples, RT-qPCR assays were carried out.

Results: A transcriptome study allowed us to identify differential miRNA gene expression between tumoral (n=28; Ta and T1 stages) and normal (n=10) tissues of BC patients (discovery cohort), thereby identifying 34 differentially expressed miRNAs. Afterwards, we validated these results by RT-qPCR using other 108 paired (normal/tumor) tissue samples, confirming upregulation and downregulation of 18 and 16 miRNAs, respectively, in tumoral tissue. Finally, we evaluated gene expression of some of these miRNAs in urine samples in order to identify biomarkers with predictive/prognostic values in liquid biopsy samples for BC.

Conclusions: Deregulation of some miRNAs allows discriminating BC patients and healthy donors using tissue samples. Several of these miRNAs have showed differential expression in urine samples, being a promising way to generate an easy, inexpensive and non-invasive way to diagnose and follow-up these patients.

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