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Table of contents

Bioinformatics analysis of prostate cancer-related microRNA panel miR-141-3p, miR-21-5p and miR-375-3p

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Abstract: Circulatory microRNAs are among the most extensively studied biomarker candidates for prostate cancer (PCa) diagnosis and monitoring through liquid biopsy. Besides their biomarker significance, regulatory properties of cell-free microRNAs became a subject of broader interest of researchers involved in the field of molecular basis of PCa. A set of circulatory microRNAs (miR-21-5p, miR-141-3p and miR-375-3p) was frequently reported as potentially valuable biomarker panel for PCa diagnosis and/or prognosis, including the extracellular vesicle (EV)-derived fraction. Since EVs act as major mediators of intercellular communication, the aim of the present study was to investigate functional properties of this microRNA panel via an *in silico* analysis. MicroRNA-mRNA network was constructed by using miRNet 2.0 with validated targets, while KEGG pathway and Gene Ontology (GO) enrichment analysis were used for exploring key biological processes (BP), cellular components (CC), and molecular functions (MF). KEGG pathway analysis revealed that the most enriched pathways are cancer-related, including the 'pathways in cancer' and 'prostate cancer'. The BP analysis highlighted enrichment in terms related to cell cycle progression and cell division, EGFR signalling and intracellular protein transport and degradation. In the MF category, the potential targets of these microRNAs were predominantly linked to activation of signalling pathways, including nucleotide binding, kinase activity and ligase activity. After cross analysing the target gene list with the downregulated differentially expressed genes in PCa from TCGA database, 70 genes remained at cross section, with the largest GO enrichment effect determined for 'Positive regulation of vascular endothelial growth factor production' process. A broader protein-protein interaction (PPI) network constructed using STRING data identified 12 hub genes, which are concentrated on two cancer-related pathway terms: 'pathways in cancer' and 'proteoglycans in cancer'. The presented results of bioinformatics analysis illustrate the biological relevance and highlight the potential functions of selected microRNA panel, supporting their possible roles as both biomarkers and regulators of malignant phenotype in PCa.

Keywords: prostate cancer, microRNA, extracellular vesicles, gene ontology.

1. Introduction

Prostate cancer (PCa), one of the most commonly diagnosed malignancies in men, presents major challenges in diagnosis and clinical management, primarily due to a suboptimal accuracy of risk stratification in PCa patients based on the usage of standard prognostic parameters [1]. Therefore, an ongoing search for validated PCa biomarkers aims to aid in the diagnostics and decision making, by improving risk estimation and enabling a more precise monitoring of the biological behaviour of the tumour. MicroRNAs from cell-free body fluids and extracellular vesicles (EVs) emerged as plausible candidates for useful PCa biomarkers, due to their stability in body fluids and regulatory role in the major cellular processes involved in prostate carcinogenesis [2]. Beside protecting microRNAs from degradation, EVs mediate their delivery to recipient cells and participate in intercellular communication essential for PCa progression. Therefore, potential PCa biomarkers may also act as modulators of cellular behaviour and exert cancer phenotype-related mechanisms in proximal or distant recipient cells. To date, results obtained by high-throughput microRNA profiling identified only a small number of microRNAs with reproducible deregulation in the circulation of PCa patients. A set of circulatory microRNAs (miR-21-5p, miR-141-3p and miR-375-3p), including the extracellular vesicle (EV)-derived fraction, was frequently reported as potentially valuable biomarker panel for PCa diagnosis and/or prognosis [3]. Since EVs act as major mediators of intercellular communication, the aim of the present study was to investigate functional properties of this microRNA panel via an *in silico* analysis.

2. Methodology

2.1. microRNA–mRNA interaction network construction

The microRNA–mRNA interaction network was constructed using miRNet2.0. and the resulting nodes (validated targets from miRTarBase 9.0 and TarBase 9.0) were subjected to GO (BP, CC and MF categories) and KEGG pathway analysis in order to characterize their biological function. GO terms and KEGG pathway enrichment analysis was performed using the hypergeometric test implemented in miRNet 2.0.

2.2. Identification of PCa-downregulated genes among microRNA targets

A panel of downregulated DEGs in TCGA-PRAD data collection was extracted using TACCO database (default $\log_2$(fold change)<-2 and ≥2, p<0.001) and a cross-section was made with the list of validated targets of miR-21-5p, miR-141-3p and miR-375-3p. The resulting gene list (n=70) was subjected to GO and KEGG pathway analysis.

2.3. Extended PPI network construction and hub gene identification

Data from STRING was used for constructing a broader PPI network applying MiRNet 2.0 (cut-off degree = 2). Hub genes were identified based on the network topology parameters (degree ≥500).

3. Results and Discussion

MiRNet 2.0 search for experimentally validated targets of miR-21-5p, miR-141-3p and miR-375-3p resulted in 9461 hits, most identified as unique targets of miR-21-5p (**Fig. 1A**). KEGG pathway analysis revealed that the most enriched pathways are cancer-related, including the 'pathways in cancer' and 'prostate cancer' (70 genes) (**Fig. 1B**).

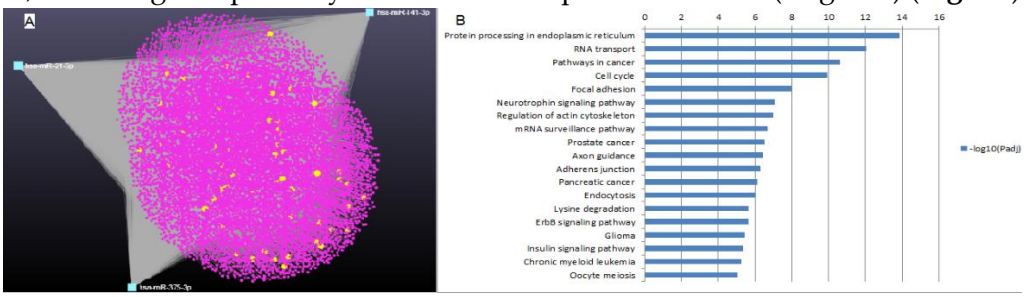

Figure 1. (A) microRNA–mRNA interaction network of miR-21-5p, miR-141-3p and miR-375-3p with "prostate cancer" pathway genes (KEGG) highlighted in yellow (n=70). (B) KEGG pathway analysis of miR-21-5p, miR-141-3p and miR-375-3p target genes.

The BP analysis highlighted enrichment in terms related to cell cycle progression and cell division, EGFR signalling and intracellular protein transport and degradation. In the MF category, potential targets of these microRNAs were predominantly linked to the activation of signalling pathways, including nucleotide binding, kinase activity and ligase activity. These results are consistent with a hypothesized role of the analysed microRNAs in the molecular basis of PCa, since enriched pathways, biological functions and molecular functions are related to carcinogenesis [4,5].

In order to investigate potential local effects of tumor-derived miR-21-5p, miR-141-3p and miR-375-3p, we conducted a cross analysis of target gene list with the downregulated differentially expressed genes (DEGs) in PCa from TCGA database (n=299) (**Fig. 2A**). This resulted in 70 genes at the cross section, for which the largest GO enrichment effect was determined for 'Positive regulation of vascular endothelial growth factor production' process (**Fig 2B**), which enhances angiogenesis and plays an important role in PCa growth and metastasis [6].

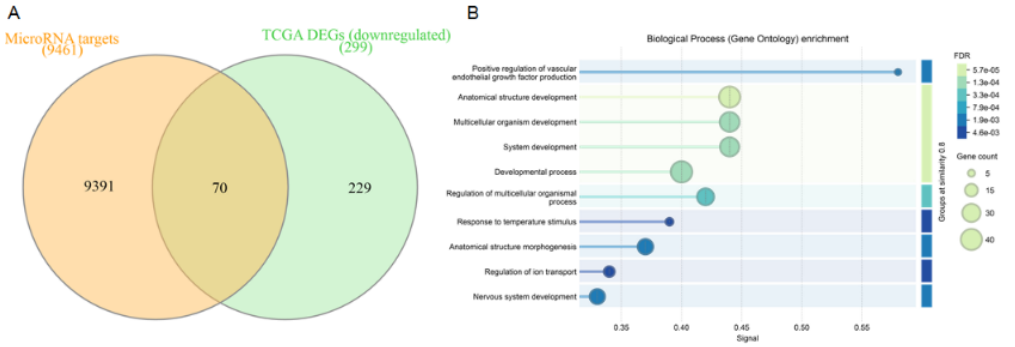

Figure 2. (A) Identification of PCa-related downregulated DEGs from TCGA (n=70). (B) GO analysis (biological process category) for miR-21-5p, miR-141-3p and miR-375-3p target genes downregulated in PCa (TCGA DEGs).

A broader protein-protein interaction (PPI) network, which incorporates genes indirectly interacting with miR-21-5p, miR-141-3p and miR-375-3p, was constructed using STRING data. This led to identification of 12 hub genes (**Fig. 3**), which are concentrated on two cancer-related pathway terms: 'pathways in cancer' and 'proteoglycans in cancer'.

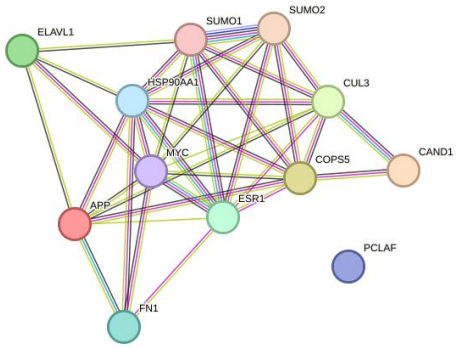

Figure 3. The STRING PPI network of the identified hub genes.

4. Conclusion

The presented results of bioinformatics analysis illustrate a biological relevance and highlight the potential functions of selected microRNA panel (miR-21-5p, miR-141-3p and miR-375-3p), supporting their possible roles as both biomarkers and regulators of malignant phenotype in PCa with potential significance as therapeutic targets. A significant portion of mRNAs downregulated in PCa tissue was experimentally validated as targets of these microRNAs.

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