Exp Oncol 2022
44, 1, 47–51

Experimental ONCOLOGY

DIFFERENTIAL EXPRESSION PATTERN OF *AIP*, *UCKL1*, AND *PKN1* GENES IN PROSTATE CANCER PATIENTS

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***Background*: The evolution of research on the therapy of prostate cancer (PC) depends on a study of molecules that are involved in the progression of this disease. Nevertheless, there is a need for additional biomarkers that would help to refine the molecular profile of PC and propose the personalized therapeutic approach. *Aim:* To study differential expression patterns of the *AIP*, *UCKL1*, and *PKN1* genes in blood sera and tumor tissue of patients with PC with different Gleason scores. *Materials and Methods:* The total extracellular RNA was isolated from blood sera of 44 PC patients and 4 healthy donors. cDNAs were synthesized and quantitative polymerase chain reaction (qPCR) was performed. Immunohistochemical study of the UCKL, AIP and PKN1 proteins was performed on deparaffinized sections of tumors. The study was supplemented by a bioinformatic analysis of the publicly available databases. *Results:* The *UCKL1, AIP, PKN1* genes were overexpressed at the mRNA level in blood sera of PC patients, compared to healthy donors. Extracellular mRNA levels of *AIP* and *UCKL-1* were 100-1000-fold increased in all PC samples compared to the healthy donors but without significant inequality between the groups of PC cases differing by the Gleason score. The highest levels were detected in the samples from PC patients with the Gleason score > 9. The *PKN1* expression was higher in PC patients compared with healthy donors but without significant difference between the groups. *Conclusions:* From the three chosen genes, *AIP* and *UCKL1* showed similar pattern of expression assessed either by extracellular mRNA levels in patient sera or the protein in PC tissues. *AIP* was up to 1000-fold increased in all PC samples, compared to the healthy donors, with the highest levels in PC cases with Gleason score > 9. Expression levels of the AIP and UCKL1 genes in the PC patient sera may be used as an additional criterion for prognosis of tumor progression.**

Key Words: **UCKL1, AIP, PKN1, prostate cancer, expression pattern, bioinformatic analysis.**

DOI: 10.32471/exp-oncology.2312-8852.vol-44-no-1.17380

Prostate cancer (PC) ranks second worldwide among the most common cancers in men after lung cancer [1, 2]. Every year, more than 7000 new cases of PC are diagnosed in Ukraine, and about 3000 patients die of this disease. According to the National Cancer Registry of Ukraine, 7758 new cases of PC were diagnosed in 2019. The PC ranks third in Ukraine among the causes of death from malignant neoplasms, after lung cancer and gastric cancer. In 2019, 3351 men died of PC [2].

It is well known that PC cells arise due to malignant transformation of prostate epithelial cells. Most deaths occur at the advanced stages of the disease due to metastasis [3, 4]. PC is diagnosed on the clinical and morphological grounds. Immunohistochemical studies are used especially to evaluate levels of such proteins as PTEN, p63, NKX3.1, prostein, keratin 7, in addition to assessing prostate specific antigen (PSA) and prostate specific acid phosphatase in serum and urine [5–9]. Nowadays, a lot of research is aimed at investigating the role of various markers of cancer stem cells, namely NANOG, CD44, CD54, and NOTCH1 [10–12]. However, the mechanisms underlying the metastasizing of malignant PC cells have been studied insufficiently. Therefore, identification of the putative prognostic biomarkers of PC is an important area for personalized medicine for better treatment of metastatic PC.

PC is most often diagnosed in men of the age between 62 and 70, so the most important is to detect the disease early and propose adequate treatment. Nevertheless, there is a growing number of malignant neoplasms diagnosed in younger patients. The problems of early, especially non-invasive diagnostics need to be addressed urgently.

In our previous work, we expanded up a range of tumor markers for breast cancer choosing few genes known to be implicated in cell transformation. Among them were aryl hydrocarbon receptor interacting protein (AIP) also known as *ARA9* and *XAP-2* (**NP_003968**), uridine-cytidine kinase 1 like 1 (*UCKL-1*) (**NP_060329.2**), and protein kinase N1 (*PKN1*, **NP_99872**) [13]. We assessed their expression at the mRNA levels in blood sera and at protein level in tumor samples. These proteins are involved in different important cellular processes. For example, AIP in somatotroph cells interacts with HSP70 family members HSPA5 and HSPA9 and, as a regulator of stress induced heat-shock protein functions, probably modulates anti-tumorigenic functions. AIP also binds SOD1, an anti-oxidative protein with anti-proliferative potential [14]. AIP can influence the tumor vasculature [15]. High levels of *UCKL-1* expression and increased activity have been detected in damaged tissues, colon tumors [16], hepatocellular carcinomas [17, 18] and in B cell transformation in Epstein — Barr virus infection [19]. PKN1 plays

Submitted: February 07, 2022.
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Abbreviation used: AIP – aryl hydrocarbon receptor interacting protein; IHC – immunohistochemical; PC – prostate cancer; PKN1 – protein kinase N1; PSA – prostate specific antigen; qPCR – quantitative polymerase chain reaction; UCKL-1 – uridine-cytidine kinase like 1.

an important role in the development and progression of liver cancer [20]. It also regulates cell migration and gene expression through its kinase activity, but does not affect cell proliferation [21].

Earlier, we have shown that it is possible to analyze the extracellular mRNA [22, 23] that could be stabilized by a placement in the specific membrane vesicles, such as exosomes (diameter < 150 μm), microvesicles (200–500 μm), oncosomes (1–10 μm), apoptotic bodies, etc. [23, 24]. Of course, such a small amount of mRNA molecules is a major problem to perform gene expression studies. On the other hand, such an approach represents a good strategy to develop non-invasive markers that could be analyzed in body fluids, such as blood, urine, saliva, or cerebrospinal fluid [25–28]. Importantly, the quantitative assessment of extracellular mRNA requires normalization with the specific control (in our case, it is *TBP*).

The aim of the present study was to analyze differential expression patterns of the *AIP, UCKL1*, and *PKN1* genes in blood sera and tumor tissue of patients with PC with different Gleason score.

MATERIALS AND METHODS

A cohort of patients. In the present study, sera and tumor tissues were collected from 44 PC patients with different Gleason score tumors treated at the National Cancer Institute of National Academy of Medical Sciences of Ukraine (Kyiv) in 2015–2017. All patients provided a written informed consent to participate in the study, which was approved by the Ethics Committee of R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of the National Academy of Sciences of Ukraine. The clinical diagnosis was based on determination of PSA in blood serum, finger rectal examination, computed tomography of the pelvic organs and/or transrectal ultrasound examination of the prostate and abdominal cavity, osteoscintigraphy, and chest radiography. In all patients, the diagnosis was verified after ultrasound-guided transrectal multifocal biopsy of the prostate. The stage of the tumor process was determined according to the International Classification of Tumors (TNM, 8th edition, 2017).

Samples. Biopsies were fixed in a neutral buffered 4% formaldehyde solution. After fixation, dehydration, and embedding in paraffin, serial 5-μm sections were stained with hematoxylin/eosin for histological diagnosis. Prostate tumors were graded based on their architectural features, according to the criteria that correspond to Gleason score, described in [29], by experienced pathologists. Samples were distributed by Gleason scores: the Gleason score ⩽ 7 (7 patients), the Gleason score > 7 (27 individuals) and patients with metastases: usually the Gleason score for those PC samples was ⩾ 9 (10 patients). Sera from 4 healthy donors were used as controls.

RNA isolation, cDNA synthesis and quantitative polymerase chain reaction (qPCR). The total extracellular RNA was isolated from serum using the RNeasy Mini Kit (Qiagen Inc, Germany), according to the manufacturer's instructions. RNA quality and quantity were checked using NanoDrop-1000 spectrophotometer. The cDNAs were synthesized using 2 μg of total RNA, M-MLV reverse transcriptase, and RNAse inhibitor (Invitrogen, USA), according to the manufacturer's protocol. Q-PCR was performed, using 2 μg cDNA and a HOT FIREPol EvaGreen qPCR Mix (Solis BioDyne, Estonia), on the PCR System 7500 (Applied Biosystem, USA). Primers were the following: for *UCKL-1* (NM_017859) forward 5'-AGCACTATGCGGGCAA GTGCTA-3', reverse 5'-TCTGGATGAGGATGGTGCCGAT-3'; for *AIP* (M_003977) forward 5'-TACTACGAGGTGCTGGACCACT-3', reverse 5'-GCACTTTGGCAAAG TCAGCCTG-3'; for PKN1 (NM_002741) forward 5'-CTGTTCGCCATC AAGGCTCTGA-3', reverse 5'-CACTGGTCACRGCCGCCAATAT-3'. As an internal control for standardization, a gene encoding TATA-binding protein (*TBP*, NM_003194) was used: forward primer 5'-TTTCTTGCCAGTCTGGAC-3', reverse 5'-CACGAACC ACGGCACTGATT-3'. Relative quantification (comparative Ct (ΔΔCt) method) was used to compare expression levels of the *UCKL-1, AIP* and *PKN1* genes with the internal control. Two or three reactions (each in triplicate) were run for each gene, so the standard deviation might be calculated.

Immunohistochemistry. Immunohistochemical (IHC) studies of UCKL, AIP and PKN1 were performed on deparaffinized tissue sections. Paraffin was dissolved in xylol, and sections were rehydrated with stepwise washing with ethanol in phosphate-buffered saline (PBS) (99; 90; 70 and 30% EtOH). Sections were then treated with the 2% solution of H_2O_2 in methanol at room temperature for 30 min to reduce background. Epitopes were exposed to a hot citrate buffer (water bath, 92 °C for 15 min). The mouse monoclonal antibodies against these proteins (Santa Cruz, USA), namely anti-AIP (anti-XAP-2) clone 35-2, anti-UCKL1 clone B-11, and anti-PKN1 clone H-4 were used diluted in blocking buffer (2% bovine serum albumin, 0.2% Tween-20, 10% glycerol, 0.05% NaN3 in PBS). The EnVision system (DAKO) was used in 30 min second-step incubation. After washing in phosphate-buffered saline peroxidase activity was assayed using DAB. After counterstaining with hematoxylin for 1–2 min, sections were dehydrated and mounted in Canadian balsam, after that the stained slides were visualized on a Leica microscope.

Bioinformatic data analysis. To analyze expression of genes at the mRNA level, a publicly available data Protein Atlas was used. Human Protein Atlas available from http://www.proteinatlas.org.

Statistical analysis. GraphPad Prism software (version 8, GraphPad Software, La Jolla, USA) was used to determine the means of the gene expression. The Kruskal — Wallis test for non-parametric criteria for the groups was performed for each gene.

RESULTS AND DISCUSSION

The relative amounts of the extracellular mRNA of the *UCKL1, AIP* and *PKN1* genes were assessed by qPCR in blood sera of 44 patients with PC and 4 healthy donors.

There was observed a difference between the expression of the selected genes in PC cases of varying malignancy grades and conditionally healthy donors. The highest level of the *UCKL1* gene was observed in patients with the highest Gleason score. (Fig. 1). Also, heterogeneous levels of *AIP* gene expression were observed in the sera of PC patients in all three groups of patients with PC of different Gleason scores, and in cancer cases they were significantly higher than in the conditionally healthy donors (Fig. 1).

The level of *PKN1* gene expression in the group of conditionally healthy donors was critically low, but there was registered an increase in the level of the gene expression, although the groups of PC patients were very heterogeneous in this respect (Fig. 1). *PKN1* expression was low in control sera and sharply increased in cancer cases with a Gleason score < 7. With increasing Gleason score, the level of *PKN1* decreased, as it was observed in patients with PC metastasis.

Using the RNAseq data, a Protein Atlas team calculated the survival probability of PC patients with gene expression above the median value (high expression) and below the median value (low expression). No significant differences were found for all three genes, even if *UCKL-1* showed a trend to be higher in patients with a poorer 5-year survival rate (Fig. 2). *PKN-1* and *AIP* cannot be considered the prognostic markers for PC, however the higher levels of PKN-1 look more favorable for the 5-year survival rate (Fig. 2).

We examined expression of the selected genes at the protein levels using IHC. The corresponding staining was detected only in cancer cells but not in stroma cells or lymphocytes. The expression of UCKL1, AIP and PKN1 was detected in all PC samples, regardless of the Gleason score. The highest level of UCKL1 expression at the protein level was found in samples from patients with the highest Gleason score (9–10) of PC (Fig. 3). It should be noted that the lowest levels of UCKL1 and PKN1 were observed in the samples of tumors with Gleason score 6, which corresponds to the data on corresponding RNA levels in the sera of PC patients.

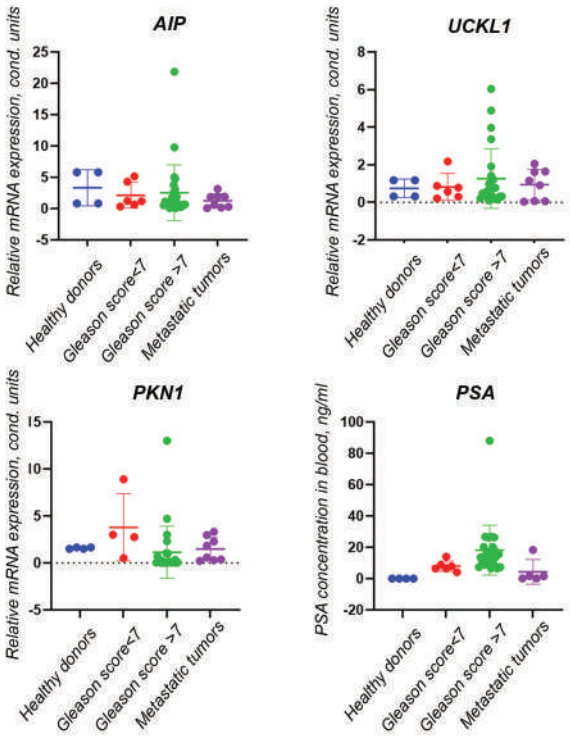

Fig. 1. Expression patterns of *UCKL1, AIP*, and *PKN1* genes at mRNA levels in blood sera assessed by qPCR. The Figure was prepared using GraphPad Prism software; the Kruskal–Wallis test for non-parametric values in groups was applied for each gene. Significant differences are considered if $p \leqslant 0.05$

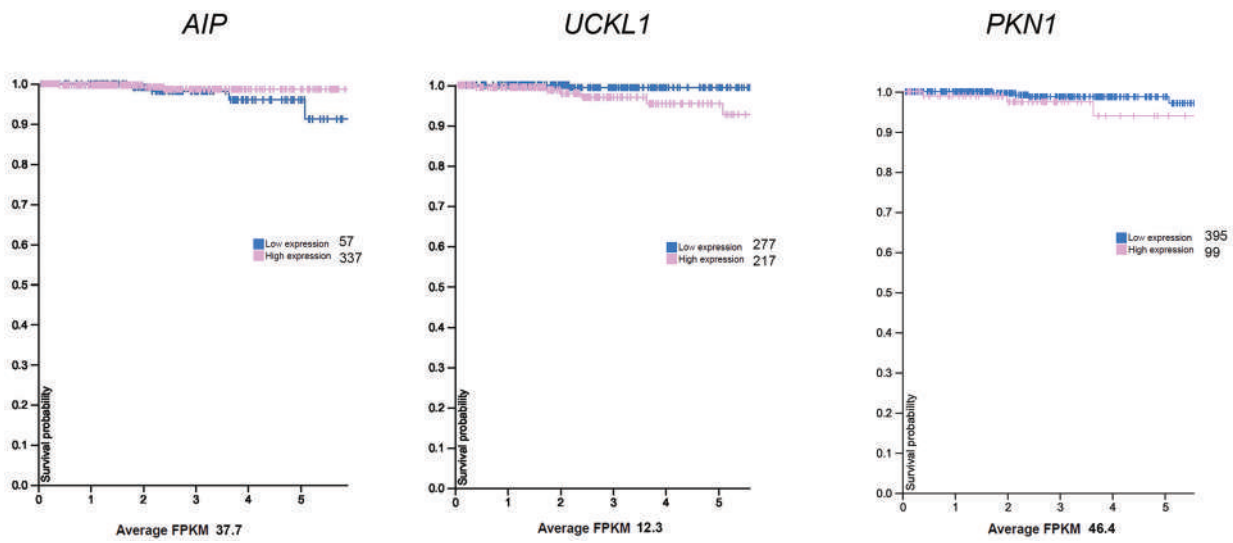

Fig. 2. Relative expression of *AIP*, *UCKL1*, and *PKN1* genes and a survival analysis (the Protein Atlas portal). Relative expression, based on RNA seq, was calculated in the FPKM units, providing a digital measure of the abundance of transcripts. AIP (www.proteinatlas.org/ENSG00000110711-AIP/pathology/prostate+cancer) and PKN1 (www.proteinatlas.org/ENSG00000123143-PKN1/pathology/prostate+cancer) are not prognostic markers, while UCKL1 (www.proteinatlas.org/ENSG00000198276-UCKL1/pathology/prostate+cancer) might be one

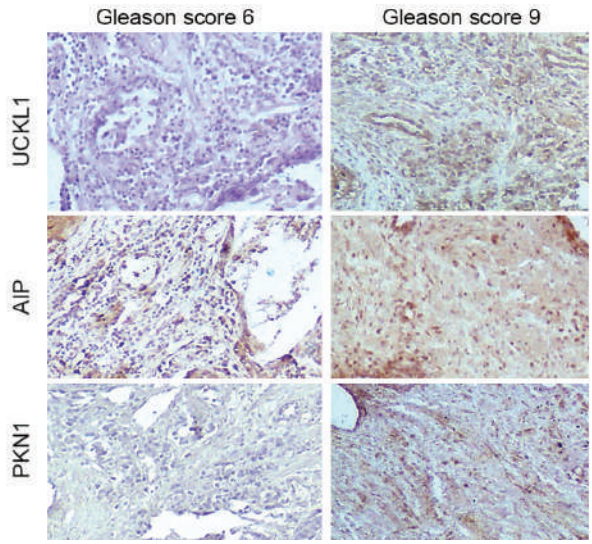

Fig. 3. Immunohistochemical staining of UCKL1, AIP and PKN1 proteins in tissue samples of PC patients with tumors of Gleason scores 6 and 9. Notice an increase of the protein signals intensity in the samples with Gleason score 9

In tumors of the Gleason score less than 7 points, all cells are close to the normal structure of prostate tissue. The basal layer of cells is present, but not clearly expressed, with a relatively small polymorphism in the cell composition. In contrast, the analyzed micrographs of PC from patients with Gleason score of 9–10 and from patients with metastases, show a pronounced infiltrative process, atypia of gland cells, clusters of undifferentiated cells. There are no lumens of the ducts of the gland. The nuclei and cells of the gland have a high degree of polymorphism. Also, stromal invasions are seen.

According to the degree of pathogenicity, PC with metastases to bone tissue (Gleason score from 7 to 10) is considered the most malignant. According to the results obtained in the present study, there is a correlation between the relative level of expression of the studied genes and the malignancy of PC, determined by Gleason score. Importantly, the data of the IHC study of prostate tissue are consistent with the results of determining the expression of the studied genes by the qPCR.

In contrast to the expression of *UCKL1* in breast cancer samples [13], expression of this gene at protein level in PC cases increases along with increasing aggressiveness of the tumor process.

From the three chosen genes, *AIP* and *UCKL1* showed similar pattern of expression regarding their extracellular mRNA levels in patient sera and the protein in PC tissues. *AIP* was up to 1000-fold increased in all PC samples, compared to the healthy donors, with the highest levels in PC cases with Gleason score $\geqslant 9$.

To assess whether expression levels of *AIP* and *UCKL1* genes in the PC patients could be used as additional markers of tumor progression, it seems reasonable to perform the similar study on a larger cohort of PC patients.

ACKNOWLEDGMENTS

This work was supported by a research program of National Academy of Sciences of Ukraine "Molecular and Biological Factors of Heterogeneity of Malignant Cells and Variability of the Clinical Course of Hormone-Dependent Tumors" (0117U002034). The authors thank Academician of the National Academy of Sciences of Ukraine V.F. Chekhun for the fruitful critical discussions on this manuscript and also the colleagues of the Research Department of Plastic and Reconstructive Oncourology of National Cancer Institute of National Academy of Medical Sciences of Ukraine, especially the head of the Department Corresponding Member of the National Academy of Medical Sciences of Ukraine Professor E.O. Stakhovsky for a collection of the clinical samples.

AUTHORS CONTRIBUTION

NL, TZ and LK carried out the immunofluorescence staining. EK and LK performed qPCR. EK and LK performed a bioinformatic and statistical analysis. NL and TZ collected PC tissue and serum samples. NL, LK and EK conceived and designed the study. NL and EK coordinated this study. LK and EK drafted the manuscript. All authors read, edited, and approved the final manuscript.

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ДИФЕРЕНЦІЙНИЙ ПАТЕРН ЕКСПРЕСІЇ ГЕНІВ *AIP*, *UCKL1* ТА *PKN1* У ЗРАЗКАХ РАКУ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ

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Еволюція досліджень щодо лікування пацієнтів з раком передміхурової залози (РПЗ) залежить від вивчення молекул, які беруть участь у прогресуванні цього захворювання. Тим не менш, існує потреба в додаткових біомаркерах, які б допомогли уточнити молекулярний профіль РПЗ та запропонувати персоналізовану терапію. ***Мета:*** Вивчити диференційну експресію генів *AIP*, *UCKL1* та *PKN1* у сироватці крові та пухлинній тканині пацієнтів з РПЗ, що характеризуються різною кількістю балів за Глісоном. ***Матеріали і методи.*** Загальну позаклітинну РНК виділяли із сироватки крові 44 пацієнтів з РПЗ. Синтезували кДНК та проводили аналіз методом кількісної полімеразної ланцюгової реакції (quantitative polymerase chain reaction — qPCR). Також на зрізах депарафінованих тканин проводили імуногістохімічні дослідження білків UCKL, AIP та PKN1. Дослідження було доповнено біоінформаційним аналізом загальнодоступних баз даних. ***Результати:*** Гени *UCKL1*, *AIP*, і *PKN1* були надекспресовані на рівні мРНК у сироватці крові пацієнтів з РПЗ порівняно зі здоровими особами. Рівні позаклітинної мРНК *AIP* та *UCKL-1* були в 100–1000 разів підвищені у всіх зразках РПЗ, порівняно зі здоровими донорами, але без значної нерівності між різними групами, сформованими згідно з балами за шкалою Глісона. Найвищі рівні було виявлено у зразках пацієнтів з балом Глісона вище 9. Експресія *PKN1* була вищою порівняно зі здоровими донорами, але без істотної різниці між зразками пацієнтів з РПЗ. ***Висновки:*** Ген *AIP* демонстрував ту саму картину експресії, що й позаклітинна мРНК у сироватці крові пацієнтів та білок у тканинах РПЗ, і рівень його експресії був до 1000 разів підвищений у всіх зразках РПЗ, порівняно зі здоровими донорами. Найвищі рівні виявлені у зразках із балом вище 9 за шкалою Глісона. Таким чином, дослідження рівнів експресії генів *AIP* та *UCKL1* у сироватках пацієнтів з РПЗ може бути використано як додатковий критерій для прогнозу прогресування пухлини та вибору хіміотерапевтичних засобів.

Ключові слова: UCKL1, AIP, PKN1, рак передміхурової залози, патерн експресії, біоінформаційний аналіз.