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ORIGINAL ARTICLE

Investigation of the association of tRNA-derived fragments (tRF-17-79MP9PP and tRF-18-79MP9P04) with prostate cancer

Sercan Ergun[1,7] · Kadir Önem[2] · Deniz Bayçelebi[3] · Ümmet Abur[4] · Özlem Terzi[5] · Senanur Olfaz Aslan[6] · Neslihan Taşkurt Hekim[1] · Sezgin Güneş[1] · Dilbeste Demir Yeşilyurt[1] · Yeda Keleş[1]

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Abstract

Introduction This study investigates the association between the levels of two tRNA-derived fragments, tRF-17-79MP9PP and tRF-18-79MP9P04, and the pathophysiology of prostate cancer (PCa).

Materials and methods Forty patients were included: 8 with benign prostatic hyperplasia (BPH) and 32 with different PCa grades. Total RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor tissues, and the levels of tRF-17-79MP9PP and tRF-18-79MP9P04 were analyzed.

Results The abundance of tRF-17-79MP9PP increased progressively with cancer grade ($p<0.001$), with the highest levels observed in advanced PCa. Interestingly, BPH also showed higher tRF-17-79MP9PP level than low- and mild-grade PCa. Level of tRF-18-79MP9P04 was comparable between BPH and low-grade PCa, but significantly higher in mild, high, and advanced grades ($p<0.001$). Furthermore, PSA levels were significantly correlated with both tRF-17-79MP9PP and tRF-18-79MP9P04 in PCa patients ($p<0.001$), but not in the BPH group.

Discussion Both tRF-17-79MP9PP and tRF-18-79MP9P04 appear to play important roles in prostate cancer, demonstrating potential oncogenic behavior in advanced stages, which contrasts with previous studies reporting tumor-suppressive effects.

Conclusion These findings indicate that elevated levels of these tRNA-derived fragments may serve as potential biomarkers for distinguishing between different grades of PCa.

Keywords Prostate cancer · TRNA-derived fragments · Expression analysis

✉ Sercan Ergun
sercanergun@msn.com; sercan.ergun@omu.edu.tr

Kadir Önem
kadironem@yahoo.com

Deniz Bayçelebi
deniz.baycelebi@omu.edu.tr

Ümmet Abur
ummetabur@hotmail.com

Özlem Terzi
ozlemzelterzi@hotmail.com

Senanur Olfaz Aslan
senanurolfaz@gmail.com

Neslihan Taşkurt Hekim
neslihan.taskurt@omu.edu.tr

Sezgin Güneş
sezgingunes@yahoo.com

Dilbeste Demir Yeşilyurt
dilbestedemir@gmail.com

Yeda Keleş
yedakelesyk@gmail.com

[1] Department of Medical Biology, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey

[2] Department of Urology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

[3] Department of Medical Pathology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkeyv, Turkey

[4] Department of Medical Genetics, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

[5] Department of Public Health, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Turkey

[6] Department of Molecular Medicine, Graduate School, Ondokuz Mayıs University, Samsun, Turkey

[7] Department of Medical Biology, Bacis Sciences Division, Faculty of Medicine, Ondokuz Mayıs University, Atakum, Samsun 55139, Turkey

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Introduction

The treatment of prostate cancer (PC) is hindered due to the lack of reliable markers and the inadequacy of treatment methods. According to global projections, prostate cancer–related deaths are expected to increase by approximately 85% from around 375,000 in 2020 to nearly 700,000 by 2040 [1]. In Turkey, between 2004 and 2018, the age-standardized mortality rate from prostate cancer increased steadily, with an average annual percent change of ~ 2.6% [2]. To discover better markers and develop new therapeutic strategies, a better understanding of the molecular mechanisms behind the onset and progression of PC is necessary. The role of small non-coding RNAs, other than microRNAs (miRNAs), in PC is not yet fully understood [3, 4].

In addition to their known roles in translation, tRNAs (~ 72 nt) can be processed to form biologically active tRNA-derived fragments (tRFs) (~ 18–50 nt). tRFs are produced by the specific cleavage of precursor tRNAs or mature tRNAs in different regions. The first information regarding tRFs dates back 40 years, when tRNA fragments were observed in cancer patients by Speer et al. [5]. However, at that time, these products were largely disregarded as non-specific degradation products. Contrary to early studies that viewed tRFs as degradation byproducts, an increasing number of recent studies have revealed the regulatory functions of tRFs. For example, tRFs can bind to Argonaute (AGO) family proteins to regulate gene expression [6, 7], increase rRNA synthesis [8], and prevent apoptosis by interacting with cytochrome [9]. They function as signaling molecules in stress responses and regulate gene expression [10, 11]. Therefore, tRFs have broad potential applications in disease diagnosis and treatment. tRFs and tiRNAs (tRNA-derived stress-induced RNAs) may affect cancer development by regulating transcription, altering mRNA stability, inhibiting translation, and regulating ribosome biogenesis [12]. tRFs can also influence cancer development by regulating cell proliferation, metastasis, apoptosis, and the cell cycle [13, 14].

Not all tRNAs are processed into tRFs, suggesting some specificity or selectivity in their biogenesis. Transfer RNAs are transcribed as a premature tRNA transcript by RNA Polymerase III. This premature structure is processed by two endonucleases, RNase P and RNase Z. The byproducts of this step (the 5'-leader and 3'-trailer sequences) may also function as tRFs within the cell. Some tRNAs carry intronic sequences in the anticodon arm that are cleaved by the SEN/TSEN complex, and the anticodon arm undergoes ligation to form the tRNA. The cleaved tRNA undergoes various modifications and folding to take on an L-shaped 3D conformation. Structurally, tRFs are classified into five groups based on the tRNA region from which they originate: tRF-5, tRF-3, i-tRF, 5'-half, and 3'-half. A study showed that the tissue-specific abundance of certain tRNAs influences the tissue-specific abundance of tRFs [15]. However, the proteins and factors involved in the processing of tRNAs into tRFs are not yet fully understood.

The tRF-18-79MP9P04, which belongs to the tRF-5 subgroup, is derived from mature tRNAVal − AAC and tRNAVal − CAC. It was found that the level of tRF-18-79MP9P04 was reduced in gastric cancer cells, and it acted as a tumor suppressor by regulating proliferation via the PTEN/PI3K/AKT signaling pathway [16]. Dubrovska et al. found that the PTEN/PI3K/Akt pathway is closely associated with prostate cancer stem cells and that PI3K could be an effective therapeutic target in prostate cancer [17]. In this context, tRF-18-79MP9P04 may hold promise for prostate cancer studies, and tRF-18-79MP9P04 has not yet been studied in prostate cancer.

The tRF-17-79MP9PP molecule, which is 17 nucleotides long, originates from the 5' mature tRNA. tRF-17-79MP9PP transcripts are found more abundantly in the cytoplasm than in the nucleus within the cell [18]. It has been observed that the level of tRF-17-79MP9PP is significantly reduced in breast cancer patients and patients with benign breast diseases compared to healthy controls [18, 19]. Additionally, it was found that the level of tRF-17-79MP9PP in tumor tissues was significantly lower compared to non-tumor adjacent tissues. The study suggests that tRF-17-79MP9PP can suppress the TGF-β1/Smad3 signaling pathway by targeting THBS1 in breast cancer cells [18]. tRF-17-79MP9PP has been shown to act as a tumor suppressor in breast cancer tissues, but it has not yet been studied in prostate cancer.

Non-coding RNAs are increasingly being recognized as key regulators of cancer, and better understanding them may provide new insights into cancer treatment. With this study, we aim to investigate the relationship between changes in the levels of two different tRFs (tRF-18-79MP9P04 and tRF-17-79MP9PP), which have been studied extensively in various types of cancer but not yet in prostate cancer tissues, and the pathophysiology of prostate cancer.

Materials and methods

Collection of retrospective samples

Formalin-fixed paraffin-embedded (FFPE) tumor tissues taken from patients who admitted to the Ondokuz Mayıs University Faculty of Medicine (OMÜTF) Urology Clinic between January 2021 and January 2022 and were diagnosed with BPH and prostate cancer by the Pathology clinic were included in the study. The study population consists of 8 benign prostatic hyperplasia (BPH) and 32 PCa patients

with gradually increased grades. Of PCa patients, 8 were lower grade (Gleason score:6), 8 were mild grade (Gleason score:7, PSA < 10), 8 were higher grade (Gleason score:7, PSA > 10), and 8 were advanced grade (Gleason score ≥ 8). After FFPE tissue samples are collected, they were stored at +4 degrees until RNA isolation. Care was taken to ensure that the demographic characteristics of the patient groups were similar.

RNA isolation and cDNA extraction from FFPE tissue samples

Sections were taken from FFPE tissue samples using a microtome device with the thickness and number specified in the kit. RNA was isolated from the obtained sections using the miRNeasy FFPE Kit (Qiagen GmbH, Hilden, Germany) protocol. All steps were carried out under RNase-free conditions, and the protocol included deparaffinization, proteinase K digestion, and DNase treatment to ensure high-quality RNA suitable for downstream applications. 5X All-In-One RT MasterMix (ABM, Richmond, BC, Canada) was used to convert the obtained RNA into cDNA. The working procedure in the kit protocol was followed. The mixtures were exposed to 25 °C for 10 min, 50 °C for 60 min, 85 °C for 5 min and 4 °C for 5 min within the reverse transcription (RT) program on the GeneAmp PCR system 9700 (Applied Biosystems, Foster City, CA). cDNAs were stored at −20 °C until Real-Time PCR was performed. When necessary, cDNAs were stored at −80 °C to extend their shelf life. Spectrophotometric method was used to determine the quantity and quality of cDNA samples obtained before Real-Time PCR experiments. Quality and quantity determination was performed using Multiskan GO spectrophotometer (Thermo Scientific, NH, USA).

tRF abundance analysis by real-time PCR

For gene expression analysis, qPCR method was applied and Rotor-Gene Q (Qiagen GmbH, Hilden, Germany) device was used for this purpose. Abundances of two different selected tRFs (tRF-18-79MP9P04 and tRF-17-79MP9PP) were performed using expression primers specifically designed for these tRFs. As an internal control, SNORD48 gene, which is an essential housekeeping gene, was used for tRF level analysis and Hs_SNORD48_1_SG QuantiTect Primer Assay (Qiagen GmbH, Hilden, Germany) was used as a primer specific to this gene. BlasTaq™ 2X qPCR MasterMix (ABM, Richmond, BC, Canada) was used in the premix prepared for gene expression analysis and qPCR reaction was performed by entering the operating conditions specified in the protocol of this kit into the Rotor-Gene Q (Qiagen GmbH, Hilden, Germany) device.

Statistical analysis

SPSS 21 program (IBM software, Pointe Claire, Quebec, Canada) was used for statistical analysis of tRFs whose levels were to be measured. Student's t test was used for pairwise comparisons and one-way variance (One Way ANOVA) test was used for more than two comparisons. A value of $p < 0.05$ was considered statistically significant and an evaluation was made at a confidence interval of 0.95. In the method based on partial amounts, the measurement values of tRFs whose level was to be measured were normalized with SNORD48. Ct (Cp, Crossing points) values were obtained in the qRT-PCR method. Using the Ct values obtained from tissues of BPH and prostate cancer patients at different stages, the relevant tRF levels were compared statistically. The following formula was used with the Ct values obtained during this comparison: $2^{-\Delta\Delta CT} = 2^{-(\Delta CT \text{ (a target sample)} - \Delta CT \text{ (a reference sample)})}$. Correlation analyses between PSA levels and tRF abundances were performed using Pearson's correlation coefficient, with $p < 0.05$ considered statistically significant. All experimental process is presented in Fig. 1.

Results

In this study, we aimed to investigate the relationship between changes in the levels of two different tRNA-derived fragments (tRF-18-79MP9P04, tRF-31-U5YKFN8DYDZDD and tRF-17-79MP9PP) and the pathophysiology of prostate cancer (PCa). The study population consisted of 8 patients with benign prostatic hyperplasia (BPH) and 32 patients with PCa of gradually increasing grade. Eight of the PCa patients were low-grade (Gleason score:6), 8 were mild-grade (Gleason score:7, PSA < 10), 8 were high-grade (Gleason score:7, PSA > 10), and 8 were advanced-grade (Gleason score ≥ 8). Total RNA including small non-coding RNAs were isolated from formalin-fixed paraffin-embedded (FFPE) tumor tissues of 40 patients with the relevant kit and the obtained RNA samples were converted to cDNA. The measured values of tRFs whose level was measured by the fractional quantification method were normalized with SNORD48. The demographic/clinical information of the patients obtained is presented in Table 1 (Table 1).

The 2-ΔCt method was used to calculate the relative fold changes of the samples. As a result, it was determined that the level of tRF-17-79MP9PP increased in direct correlation to the increasing cancer grade ($p < 0.001$) although BPH group had higher level of tRF-17-79MP9PP than lower, mild, and higher grades. Also, the level of tRF-17-79MP9PP in advanced grade was statistically significantly higher than other study groups ($p < 0.001$) (Fig. 2).

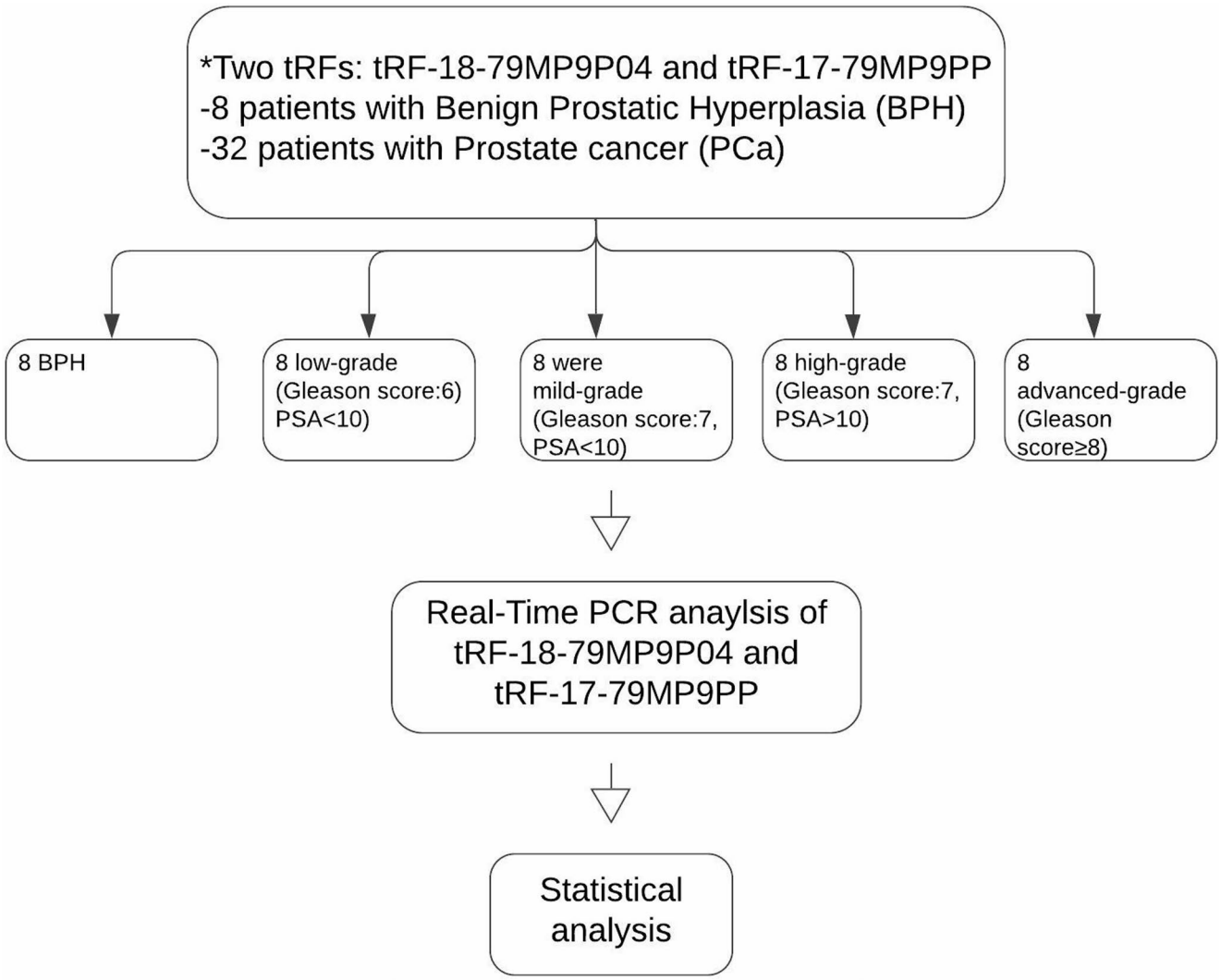

Fig. 1 Schematic overview of the experimental workflow This figure illustrates the overall design of the study, including patient group selection, sample collection, RNA isolation from FFPE prostate tissues, cDNA synthesis, and quantitative PCR analysis. The figure summarizes the comparison of tRF-17-79MP9PP and tRF-18-79MP9P04 expression levels among benign prostatic hyperplasia (BPH) and prostate cancer groups of increasing Gleason grades (low, mild, high, and advanced)

Table 1 Demographic/clinical information of patients

Group	BPH	Lower grade (Gleason score 6)	Mild grade (Gleason score:7, PSA < 10)	Higher grade (Gleason score:7, PSA > 10)	Advanced grade (Gleason score ≥ 8)
n	8	8	8	8	8
Age	71.37	54.75	62.62	66.5	62.37
Mean	58–81	47–64	54–71	60–76	53–70
Range					
PSA	4.45	6.31	6.61	17.1	13.06
Mean	0.9–11.5	1.7–12	4.6–8.4	11–25.2.2	1.5–41
Range					

Also, it was observed that the levels of tRF-18-79MP9P04 were similar in BPH and low-grade groups, but mild, high and advanced grades had statistically significantly higher tRF-18-79MP9P04 levels than BPH and low-grade groups ($p < 0.001$) (Fig. 3).

According to the correlation analysis of the whole study population, PSA levels showed a statistically significant positive correlation with tRF-17-79MP9PP ($r = 0.65$, $p < 0.001$) and tRF-18-79MP9P04 ($r = 0.09$, $p < 0.001$). When analyzed within subgroups, no significant correlation was found in the

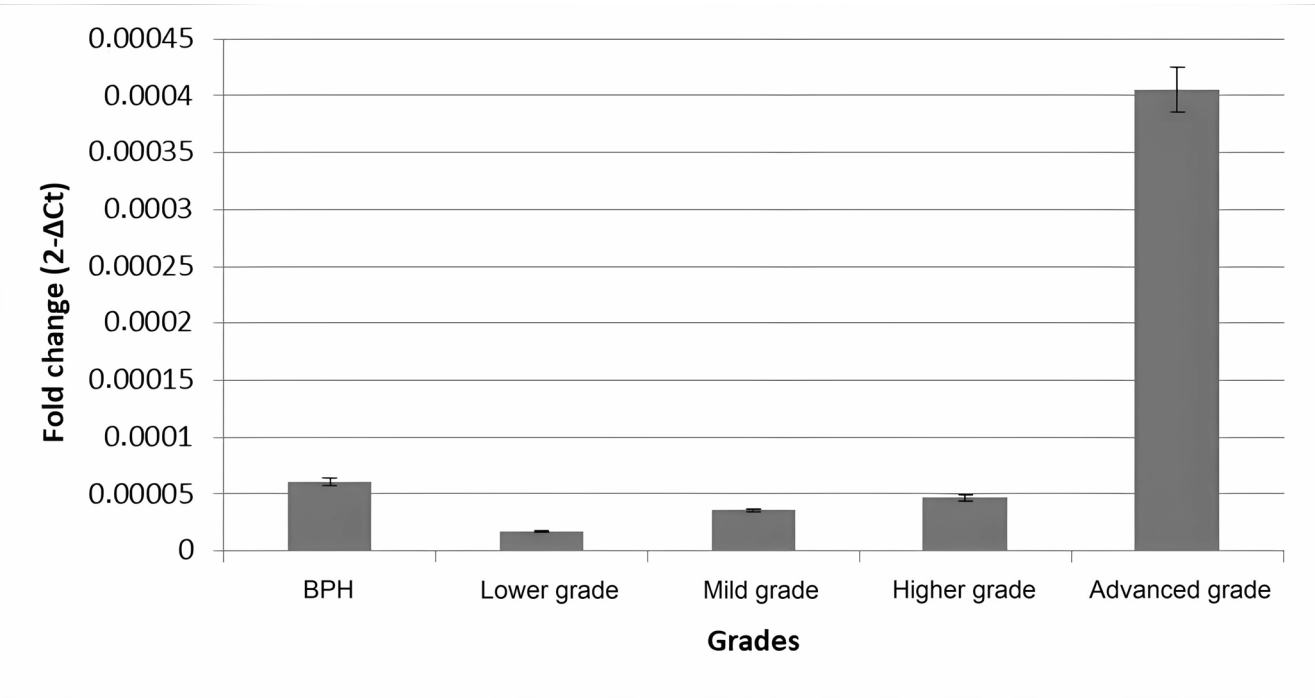

Fig. 2 Relative levels of tRF-17-79MP9PP among patient groups with different prostate pathologies The box plots show the normalized level (2−ΔCt) of tRF-17-79MP9PP in FFPE tissues from BPH ($n=8$), low-grade (Gleason 6, $n=8$), mild-grade (Gleason 7, PSA < 10, $n=8$), high-grade (Gleason 7, PSA > 10, $n=8$), and advanced-grade (Gleason ≥ 8, $n=8$) prostate cancer patients

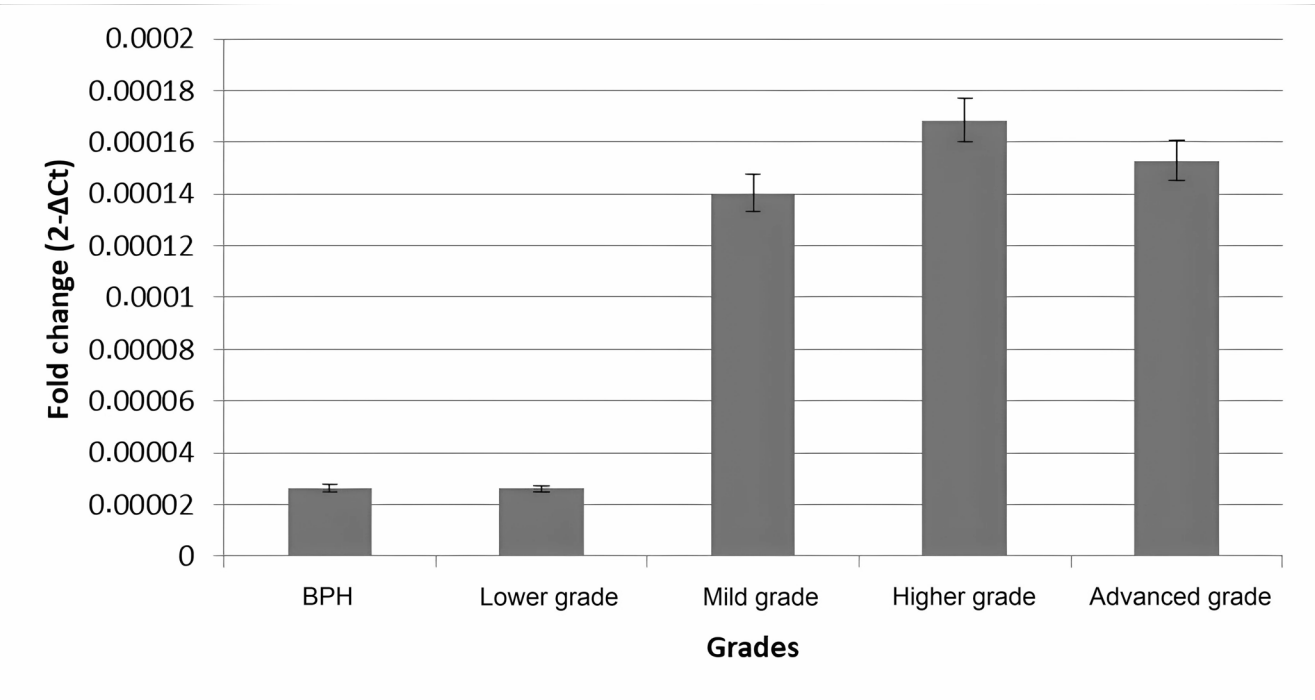

Fig. 3 Relative levels of tRF-18-79MP9P04 among patient groups with different prostate pathologies The box plots show the normalized level (2−ΔCt) of tRF-18-79MP9P04 in FFPE tissues from BPH ($n=8$), low-grade (Gleason 6, $n=8$), mild-grade (Gleason 7, PSA < 10, $n=8$), high-grade (Gleason 7, PSA > 10, $n=8$), and advanced-grade (Gleason ≥ 8, $n=8$) prostate cancer patients

BPH group ($p>0.05$). However, PSA levels demonstrated significant positive correlations with tRF-17-79MP9PP in the lower grade ($r=0.93$, $p<0.001$), mild grade ($r=0.73$, $p<0.001$), and higher grade ($r=0.55$, $p<0.001$) groups, while a weaker but still significant correlation was observed in the advanced grade group ($r=0.45$, $p<0.05$). Study data suggest that higher levels of tRF-17-79MP9PP and tRF-18-79MP9P04 may provide potential for the differential diagnosis of PCa, especially for higher grades.

Discussion

Prostate cancer is a common malignancy in men and remains a major health concern worldwide. In recent years, non-coding RNAs have gained increasing attention due to their regulatory roles in cellular processes and their involvement in cancer development and progression, including prostate cancer [20, 21]. Among these, transfer RNA–derived fragments (tRFs) have emerged as important molecules generated from tRNA cleavage, with functions in translation, gene expression regulation, and stress responses [22, 23]. Specific tRFs have shown tumor-suppressive roles in different cancers; for instance, tRF-17-79MP9PP has been reported to inhibit the TGF-β1/Smad3 pathway by targeting THBS1 in breast cancer [18, 19], while tRF-18-79MP9P04 suppresses gastric cancer cell proliferation via the PTEN/PI3K/AKT pathway [16]. Since the PTEN/PI3K/AKT pathway is closely associated with prostate cancer stem cells [17], both tRF-17-79MP9PP and tRF-18-79MP9P04 may hold promise as potential biomarkers and therapeutic targets in prostate cancer, though their roles remain largely unexplored.

In our cohort, PSA values were unexpectedly higher in the high-grade group compared to the advanced group. We consider this to be related to the limited sample size ($n=8$ per group) and inter-individual variability, since PSA levels are known to fluctuate with tumor biology and volume, and do not always correlate directly with Gleason score. Additionally, the mean age was higher in the BPH group than in the prostate cancer groups, which is in line with the natural history of BPH as it predominantly affects older men, while prostate cancer can present at relatively younger ages. These findings highlight the importance of interpreting PSA levels and age distribution within the clinical context and with larger patient cohorts.

In this study, it was determined that the level of tRF-17-79MP9PP increased in direct proportion to the increasing cancer grade ($p<0.001$) although BPH group had higher level of tRF-17-79MP9PP than lower, mild, and higher grades. Also, the level of tRF-17-79MP9PP in advanced grade was statistically significantly higher than other study groups ($p<0.001$) (Fig. 2). Moreover, it was observed that the levels of tRF-18-79MP9P04 were similar in BPH and low-grade groups, but mild, high and advanced grades had statistically significantly higher tRF-18-79MP9P04 levels than BPH and low-grade groups ($p<0.001$) (Fig. 3).

According to the correlation analysis of all the study population, there was a statistically significant positive correlation between PSA levels and levels of both tRF-17-79MP9PP and tRF-18-79MP9P04, separately ($p<0.001$). When we analyzed this correlation within the groups, there was no significant correlation in BPH group ($p>0.05$) however there were significant positive correlation for lower ($p<0.001$), mild ($p<0.001$), higher ($p<0.001$) and advanced grades ($p<0.05$).

When we compare our study findings with the studies in the literature in which tRF-17-79MP9PP and tRF-18-79MP9P04 were analyzed, there is a significant difference. When we look at the studies in the literature, we see that tRF-17-79MP9PP and tRF-18-79MP9P04 assume a tumor suppressor role, but in our study, they assume a potential oncogenic role with increased levels in advanced stages of prostate cancer. We can explain this by the fact that, like non-coding RNAs in general, they have a very sensitive regulation and can play very different roles in different cancers. Non-coding RNAs can exhibit a dual role in cancer progression by functioning as both tumor suppressors and oncogenes, depending on the cellular context [24–26]. For example, miR-21 is well-known for its oncogenic role in many cancers [27], where it promotes cell proliferation and inhibits apoptosis by targeting tumor suppressor genes such as PTEN [28]. Similarly, long non-coding RNA HOTAIR is frequently described as an oncogene that promotes metastasis and cancer progression by altering chromatin structure [29], but in some contexts, it has been shown to exhibit tumor-suppressive functions by inhibiting cell migration and invasion [30]. This dual functionality is also observed in tRNA-derived fragments (tRFs), which can either suppress tumor growth by inhibiting oncogenic signaling pathways or support cancer progression by modulating cellular stress responses [23]. The ability of ncRNAs to function in both suppressive and oncogenic roles underscores their complexity and potential as therapeutic targets in cancer treatment.

Transfer RNA–derived fragments (tRFs) have been reported to act either as tumor suppressors or as oncogenic regulators depending on the cancer type and cellular context. Recent comprehensive reviews and pan-cancer analyses document this context dependency and summarize multiple mechanisms by which tRFs influence cancer biology, including miRNA-like targeting, interaction with RNA-binding proteins, modulation of translation and stress responses, and effects on signalling pathways relevant to malignancy [31]. In prostate cancer specifically, tumour

biology is shaped by androgen receptor signalling, frequent alterations in the PTEN/PI3K/AKT axis, and a distinct tumour microenvironment; these factors can alter both tRNA processing and the downstream impact of tRFs, causing the same tRF species to exert different phenotypic effects compared with other tumour types. For example, tRF signatures have been linked to prostate cancer diagnosis and grade in recent studies, supporting disease-specific roles for certain tRFs [32]. Taken together, our observation of increased tRF-17-79MP9PP and tRF-18-79MP9P04 levels in higher-grade prostate tumours may reflect (i) disease-specific induction of tRF biogenesis, (ii) differential stability/clearance of particular tRFs in the prostate tumour milieu, or (iii) oncogenic functions of these tRFs in the prostate context (for example via modulation of PI3K/AKT or other prostate-relevant pathways). We therefore emphasise that functional studies (gain-/loss-of-function, parent-tRNA expression assessment and pathway assays) are required to clarify causality and mechanism [33].

We also observed increased tRF levels in BPH patients, and it is possible that age plays a contributory, though noncausal, role in this finding. Aging can influence RNA processing, turnover, and cleavage pathways, potentially altering tRF biogenesis or stability. Indeed, studies have documented age-dependent alterations in tRNA-derived small RNAs (tsRNAs) consistent with dysregulated RNA cleavage and stress responses in aging tissues [34]. Moreover, the prostate undergoes molecular changes with age — including variations in androgen receptor signalling, epithelial–stromal cell interactions, and gene expression programs — which may modulate the baseline level of small RNAs even in the absence of malignancy [35]. In addition, age-associated increases in prostate inflammation and immune cell infiltration in BPH could influence local RNA processing environments, potentially affecting tRF levels [36]. Finally, technical factors such as FFPE sample degradation over time or differential RNA quality in older tissues might partially contribute to observed higher tRF signals. Although our design does not allow us to disentangle these effects, we believe future studies with age-matched controls and mechanistic assays (e.g. parent tRNA expression, RNA integrity assessment) are needed to clarify the influence of aging on tRF levels in both benign and malignant prostate tissues.

As a limitation of the study, we analyzed the roles of tRF-17-79MP9PP and tRF-18-79MP9P04 in PC pathophysiology through transcriptional activity. However, there are thousands of tRF targets in the cell, so this pathway and its interactions may have many different regulators. Therefore, conducting functional analyses will enable us to cover all these interactions and reach more realistic conclusions regarding the role of tRFs in the pathophysiology of prostate cancer. Furthermore, another limitation of our study is the relatively small number of cases per group ($n=8$). Although strict inclusion criteria were applied to minimize variability and statistical analyses still revealed significant differences, larger sample sizes will be required in future studies to further validate and strengthen these findings. Moreover, changes in tRF levels may be influenced by the abundance or degradation of parent tRNAs, and highlighting the evaluation of parent tRNA levels as an important direction for future studies.

Conclusion

All in all, higher levels of tRF-17-79MP9PP and tRF-18-79MP9P04 could be valuable for distinguishing prostate cancer. These elevated levels might be particularly useful for identifying higher-grade tumors. Thus, they have potential as biomarkers in the differential diagnosis of prostate cancer.

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Author contributions S.E., S.O.A. N.T.H. and S.G. wrote the main manuscript text. S.O.A., D.D., and Y.K. prepared Figs. 1, 2 and 3. K.Ö., D.B., Ü.A. and Ö.T. contributed to data collection and analysis. All authors reviewed and approved the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Approval of the research protocol by an institutional reviewer board The study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee (Approval no: 2021/617) (Supplementary 1).

Informed consent N/A.

Registry and the registration No. of the study/trial N/A.

Animal studies N/A.

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