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ORIGINAL RESEARCH

# Elevated Expression of STAT6, ERG, and miR-647 Expression as Predictive Biomarkers for Prostate Cancer

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**Aim:** The aim of this study was to investigate the clinical significance of STAT6, ERG, miR-647 in prostate cancer (PCa).

**Methods:** This was a retrospective study. There were 210 consecutive patients diagnosed with prostate cancer or benign prostatic hyperplasia in our hospital from July 2020 to July 2023. Among those patients, 108 patients pathologically diagnosed as prostate cancer were divided into the prostate cancer group (PCa group), and 102 patients pathologically diagnosed as having benign prostatic hyperplasia were divided into the benign prostatic hyperplasia group (BPH group).

**Results:** The levels of STAT6 mRNA, ERG mRNA, and miR-647 expression in prostate cancer tissue were higher than those in BPH tissues, with statistically significant differences ($P<0.05$) . The levels of STAT6 mRNA, ERG mRNA, and miR-647 indicators in prostate cancer patients were not significantly different with respect to patient age and tumor size ($P > 0.05$) but were related to lymph node metastasis, T stage, and Gleason score ($P < 0.05$). On the other hand, the tPSA/fPSA had significantly different between two groups ($P < 0.05$). PCa group had smaller MRI sagittal diameter and anteroposterior diameter in comparison to BPH group ($P < 0.05$), furthermore, PCa group had larger PI-RAD in comparison to BPH group ($P < 0.05$).

**Conclusion:** The higher level of STAT6, ERG, and miR-647 in prostate tissue are closely related to the occurrence of prostate cancer and have certain value in predicting the onset of prostate cancer.

**Keywords:** prostate cancer, signal transducer and activator of transcription 6, ETS-related gene, miR-647, Prostate cancer

## Introduction

Prostate cancer (PCa) is a leading cause of cancer-related mortality and the second most common male malignancy worldwide.[1] In 2020, approximately 1.41 million new cases were diagnosed, accounting for 7.3% of global cancer cases and 3.8% of cancer-related deaths.[2–4] Early-stage prostate cancer often presents without clear symptoms, but as the disease progresses, issues like difficulty urinating may arise. By the time of diagnosis, many patients are in the advanced stages, where treatment outcomes are generally poor, and the mortality rate remains high. This highlights the importance of early diagnosis for better prognosis and treatment outcomes.[5] Given the complexity of prostate cancer, recent research has focused on molecular biomarkers such as microRNAs, STAT signaling pathways, and the ERG gene. These factors have shown potential in understanding the molecular mechanisms driving PCa progression and could be critical in developing more effective diagnostic and therapeutic strategies.

MicroRNAs (miRNAs), as an important molecule that has been proven to be closely related to tumorigenesis and development, have potential value in tumor diagnosis, treatment and prognosis, and are currently the focus of tumor research.[6] MiR-647 is an important member of the miRNA family and is closely related to the occurrence and development of prostate cancer. It can affect key biological processes such as the proliferation, apoptosis, invasion and

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metastasis of prostate cancer cells by regulating the expression of a series of downstream target genes.[7,8] A study had demonstrated that LncRNA PROX1-AS1 promotes proliferation, invasion, migration in prostate cancer via targeting miR-647.[9] Moreover, Chen et al[10] found that Circular RNA CircNOLC1, Upregulated by NF-KappaB, Promotes the Progression of Prostate Cancer via miR-647/PAQR4 Axis. The dysregulation of miRNA expression levels runs through the early to late stages of prostate cancer, and the miRNA-based prostate cancer treatment method may become a new technology for prostate cancer gene therapy.[11,12] Therefore, more research is needed to prove miR-647 significance in prostate cancer and provide stronger evidence for the precise diagnosis and treatment of prostate cancer.

Signal transduction and activator of transcription (STAT) is a potential cytoplasmic transcription factor that responds to cytokines to activate gene transcription and is widely distributed in tissues and cells.[13] STAT6, in particular, plays a crucial role in regulating cell growth, differentiation, and apoptosis, and it is involved in key processes such as tumorigenesis, inflammation, and immune responses.[14] While STAT6 is recognized for its significance in cancer, including its involvement in promoting tumor progression through the activation of specific gene expression pathways, its precise mechanisms in prostate cancer (PCa) remain underexplored. Previous studies have indicated that STAT6 may influence the tumor microenvironment in PCa by modulating immune cell infiltration and inflammatory responses, which are critical to cancer progression. Su et al found that STAT6 polymorphism was correlated with gefitinib-induced diarrhea in patients with non-small cell lung cancer,[15] but more detailed research is needed to understand how STAT6 specifically contributes to PCa development. Incorporating these insights into the background can add depth and provide a more comprehensive context for the role of STAT6 in prostate cancer.

The ERG gene encodes a protein that belongs to the ETS family of transcription factors.[16] These transcription factors are involved in regulating the expression of a large number of genes, thereby influencing cell growth, differentiation, and development.[17] Alterations or mutations in the ERG gene can have significant implications. In some cancers, such as certain types of leukemia and prostate cancer, abnormal activation or overexpression of the ERG gene has been observed.[18] This dysregulation can contribute to the oncogenic process by promoting cell proliferation, inhibiting apoptosis, and influencing other aspects of tumorigenesis.[19] At present, the function of ERG in prostate cancer (PCa) is not fully understood, and much of the research on its role in the initiation and progression of PCa remains in its early stages. Specifically, the mechanisms through which ERG contributes to the malignancy of PCa are still unclear, such as whether it influences the tumor microenvironment or interacts with other signaling pathways to drive tumor growth. This study aims to address these gaps by investigating the molecular interactions of ERG in PCa and exploring how its expression correlates with clinical outcomes, thus providing a clearer understanding of its role in the progression and prognosis of PCa.

MiR-647, STAT6, and ERG have shown promising potential as biomarkers in prostate cancer (PCa), not only for diagnostic purposes but also for their therapeutic and prognostic implications. miR-647, a microRNA, has been implicated in regulating various signaling pathways involved in tumorigenesis, and its expression levels have been linked to tumor progression and metastasis. Therapeutically, modulating miR-647 expression could offer a novel approach to inhibit cancer cell proliferation and metastasis, potentially improving treatment outcomes. Similarly, STAT6, a transcription factor involved in immune regulation and cell survival, has emerged as a key player in PCa progression. Given its role in tumor immune evasion and inflammation, targeting STAT6 may provide a strategy for enhancing anti-tumor immunity or overcoming resistance to therapies. Additionally, ERG, a gene commonly overexpressed in PCa, plays a significant role in gene regulation, and its dysregulation has been associated with cancer cell proliferation and survival. As such, ERG expression could serve as a prognostic marker, providing insight into the aggressiveness of the disease and the likelihood of recurrence. In clinical practice, integrating these markers into routine diagnostic and prognostic evaluations could improve personalized treatment strategies, allowing for more accurate risk stratification and targeted therapies.

This study aims to explore the expression levels of STAT6, ERG, and miR-647 in prostate tissue, with the goal of providing new molecular markers for early diagnosis and treatment of prostate cancer.

# Methods

## Study Population

In this retrospective study, we collected data of 210 consecutive patients diagnosed with prostate cancer or benign prostatic hyperplasia in our hospital from July 2020 to July 2023. Among those patients, 108 patients pathologically diagnosed as prostate cancer were divided into the prostate cancer group (PCa group), and 102 patients pathologically diagnosed as having benign prostatic hyperplasia were divided into the benign prostatic hyperplasia group (BPH group). Additionally, the study was approved by the Ethics Review Board of Huadong Hospital, Fudan University. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

## Inclusion and Exclusion Criteria

Inclusion criteria was as follow: 1) All the patients in the PCa group selected in this institute were diagnosed as PCa after prostate biopsy or surgery after hospitalization to obtain the pathological results.[20] All the patients in the BPH group were diagnosed as BPH through prostate biopsy or surgery to obtain the pathological results;[21] 2) Age ≥60 years old; 3) Patients without heart, liver, kidney, and hematopoietic system disorders or other functional impairments.

Exclusion criteria was as follow: 1) Patients with other systemic tumors and those with prostate metastasis from other tumors; 2) PCa patients who have already been treated with drugs, surgery or other means; 3) Patients with a family history of hereditary diseases.

## Immunohistochemistry (IHC)

Briefly, the paraffin-submerged tissues were sliced (5 μm thick), tagged at 4°C with the monoclonal human STAT6 and ERG antibody (dilution 1:1000, Proteintech) overnight, stained via staining kit (Zhongshan Biotechnology, Beijing, China), visualized, and then the staining score was assessed based on color intensity and positive cell rate. An average intensity score of ≥4 indicated high expression, and <4 depicted no or low expression.

## Quantitative Polymerase Chain Reaction (qPCR)

Comparison of STAT6 mRNA, ERG mRNA levels, and miR-647 expression levels between prostate cancer tissue and adjacent non-cancerous tissue were conducted using fluorescence quantitative PCR technology. Tissue RNA was extracted using a kit (QIAGEN, Germany), RNA quality was measured using an N50 microspectrophotometer (IMPLEN, Germany), RNA was reverse transcribed into cDNA according to the instructions of the reverse transcription kit (Vazyme, China), diluted to equal concentration, and SYBR quantitative PCR reaction mixture (Applied Biosystems, USA) was prepared for amplification on an Mx3005P QPCR instrument (Agilent, USA). Using GAPDH gene as the reference, the primer sequences were: STAT6 upstream primer: 5′-LAGGAGAGCAGGGGAAAGGAAG-3′, STAT6 downstream primer: 5′-LTGGCAGGTGGTGGAACTCTT-3′; using GAPDH gene as the reference, ERG primer sequences were: ERG upstream primer: ERG-F5′-TTATCGTGCCAGTAGCAGGT-3′, ERG downstream primer: ERG-R5′-GATGTTGACGTCTGGAAGGC-3′; using U6 as the reference, miR-647 upstream primer: 5′-CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGGAAGGAAG-3′, downstream primer: 5′-ACACTCCAGCTGGGGTGGCTGCACTCACT-3′, miR-647 expression was calculated using the 2-ΔΔCt method, and both reference genes and primers were synthesized and provided by Guangzhou Xingzhi Biotechnology Co., Ltd.

## Data Collection

Collect clinical information from each subject in our clinical electronic medical record database, including age, BMI (body mass index), tumor size, Gleason score, serum tPSA (total Prostate Specific Antigen), fPSA (free Prostate Specific Antigen), MRI sagittal diameter, MRI anteroposterior diameter, MRI transverse diameter, PI-RAD and ISUP classification.

## Statistical Analysis

In this study, SPSS25.0 statistical software was used for statistical analysis. For measurement data, ANOVA or *t*-test was conducted for the data that met the normal distribution and homogeneity of variance conditions, and the measured values

**Table 1** Comparison of Baseline Data Between Two Groups

| | PCa Group (n=108) | BPH Group (n=102) | χ2/t | P |
|---|---|---|---|---|
| Age | 70.31±7.37 | 69.37±8.49 | 0.860 | 0.391 |
| BMI | 24.56±0.78 | 24.35±1.55 | 1.296 | 0.196 |
| Tumor size | 1.22±0.24 | 1.20±0.32 | 0.722 | 0.471 |
| Gleason score | | – | – | – |
| ≤6 | 34(31.48%) | – | – | – |
| 7 | 46(42.59%) | – | – | – |
| ≥8 | 28(25.93%) | – | – | – |
| ISUP classification | | – | – | – |
| I | 6(10.34%) | – | – | – |
| II | 34(31.48%) | – | – | – |
| III | 34(31.48%) | – | – | – |
| IV | 26(24.07%) | – | – | – |
| V | 8(13.80%) | – | – | – |

of each index were expressed as "mean ± standard deviation (Mean ± SD)"; for data that did not meet the normal distribution, non-parametric rank sum test was used, and the measured values of each index were expressed as "median (25% percentile, 75% percentile) (M (P25.P75))"; chi-square test was used for count data. All data were rounded to two decimal places after the decimal point, and $P < 0.05$ was considered statistically significant.

# Results

## Comparison of Baseline Data Between Two Groups

In our study, there was no significant difference between two groups in terms of age, BMI, tumor size ($p > 0.05$)(Table 1).

## Immunohistochemical Staining of STAT6 and ERG

Membranous and cytoplasmic staining of ERG could be assessed in patients with prostate cancer (Figure 1). Patients with prostate cancer showed positive staining for ERG. ERG is highly expressed in Gleason scores of 7–9 and ISUP grades of III–IV. However, there was no STAT6 nuclear staining in human BPH tissues and Pca tissues (Figure 2).

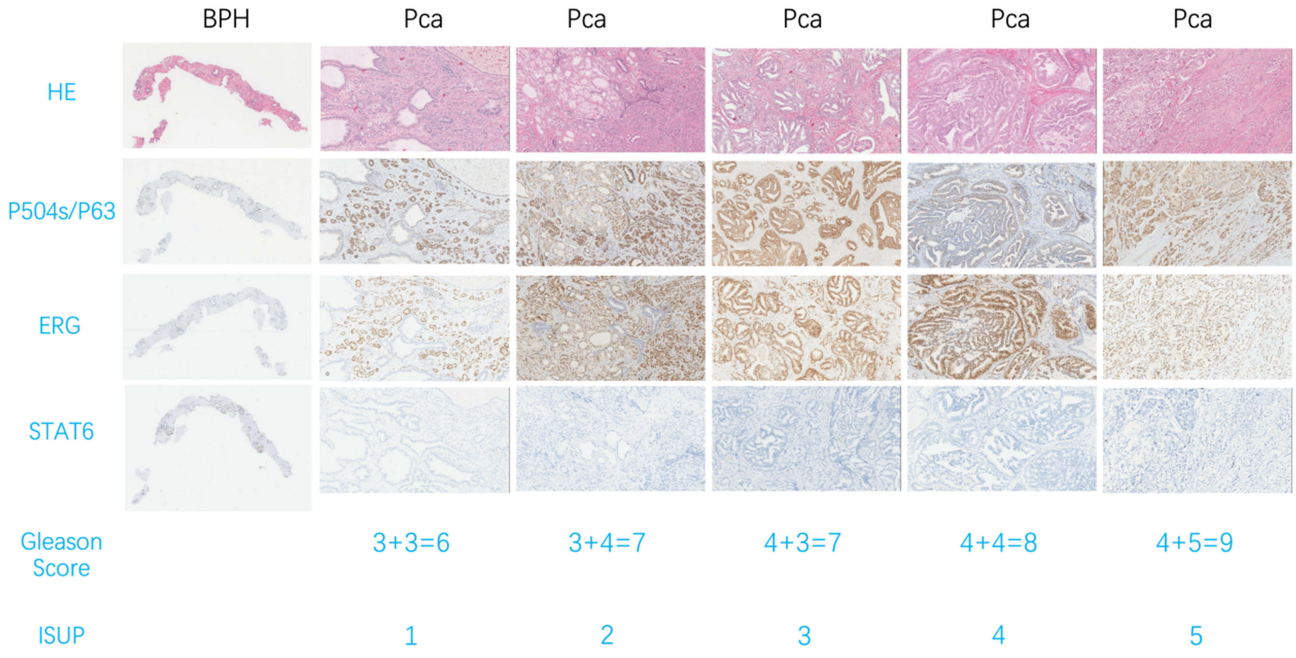


**Figure 1** Representative IHC staining of STAT6 and ERG in human BPH tissues and Pca tissues.

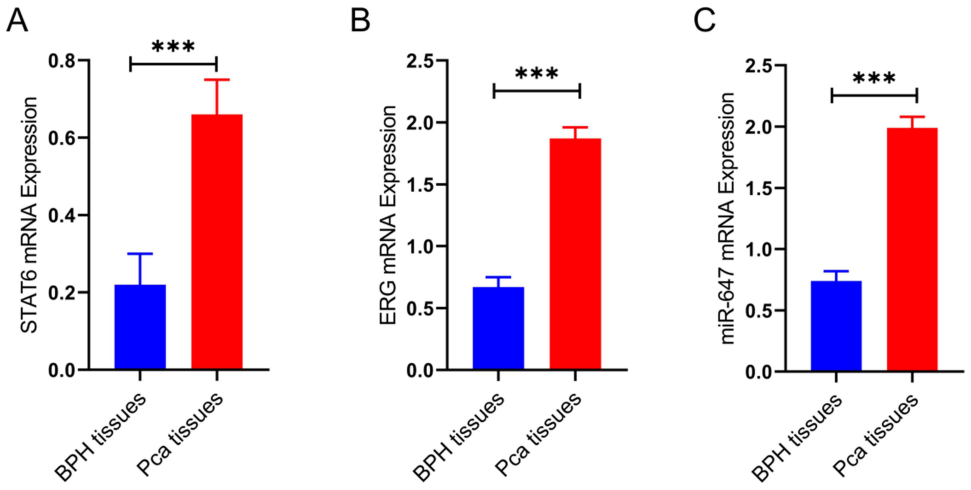


**Figure 2** Comparison of STAT6 mRNA, ERG mRNA Levels, and miR-647 Expression Levels between BPH tissues and Pca tissues. (**A**) STAT6, (**B**) ERG, (**C**) miR-647. *** P<0.05.

## Comparison of STAT6 mRNA, ERG mRNA Levels, and miR-647 Expression Levels Between BPH Tissues and Pca Tissues

The qPCR results showed that STAT6 mRNA, ERG mRNA, and miR-647 expression in Pca tissues were all higher than those in BPH tissues, with statistically significant differences ($P < 0.001$, Figure 3).

## Comparison of STAT6 mRNA, ERG mRNA, and miR-647 Indicators Among Prostate Cancer Patients with Different Clinical Pathological Features

The levels of STAT6 mRNA, ERG mRNA, and miR-647 indicators in prostate cancer patients were not significantly different with respect to patient age and tumor size ($P > 0.05$) but were related to lymph node metastasis, T stage, and Gleason score ($P < 0.05$, Table 2).

## Comparison of Serum Prostate-Specific Antigen Between Two Groups

Compared with BPH group, the serum fPSA and tPSA of the PCa group had increased in the PCa group, but there were not significantly different ($P > 0.05$). On the other hand, the tPSA/fPSA had significantly different between two groups ($P < 0.05$)(Figure 3).

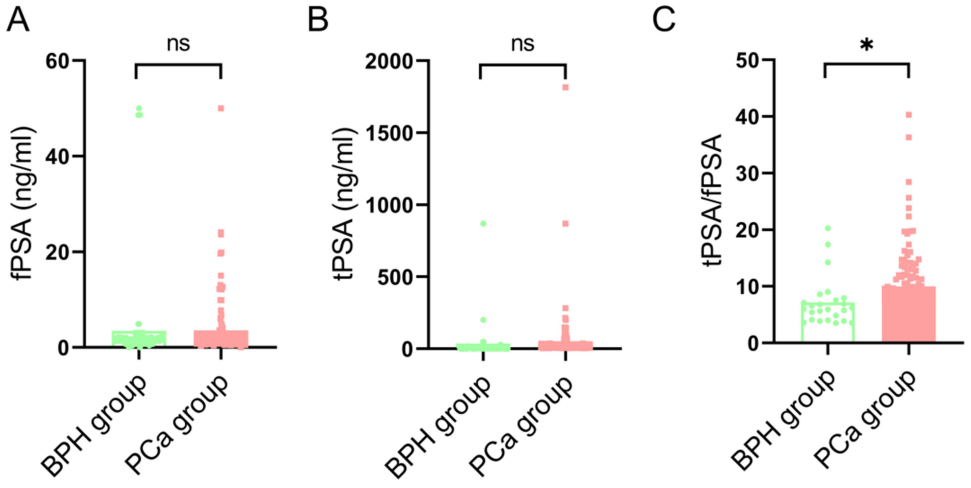


**Figure 3** Compare the levels of serum prostate-specific antigen in the two groups. (**A**) fPSA, (**B**) tPSA, (**C**) tPSA/fPSA. *P<0.001.
**Abbreviations**: fPSA, free Prostate Specific Antigen; tPSA, total Prostate Specific Antigen.


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**Table 2** Comparison of STAT6 mRNA, ERG mRNA, and miR-647 Indicators Among Prostate Cancer Patients with Different Clinical Pathological Features

| Indicators | STAT6 | t | P | ERG | t | P | miR-647 | t | P |
|---|---|---|---|---|---|---|---|---|---|
| Age | | 0.378 | 0.706 | | 0.289 | 0.773 | | 1.638 | 0.104 |
| >70yrs (61 cases) | 0.61±0.10 | | | 1.93±0.21 | | | 1.75±0.25 | | |
| >60yrs, ≤70yrs (47 cases) | 0.61±0.5 | | | 1.91±0.19 | | | 1.67±0.21 | | |
| Tumor Size | | 1.827 | 0.070 | | 0.164 | 0.870 | | 0.959 | 0.339 |
| ≥3cm (59 cases) | 0.53±0.05 | | | 1.89±0.19 | | | 1.86±0.22 | | |
| <3cm (49 cases) | 0.55±0.06 | | | 1.89±0.15 | | | 1.82±0.21 | | |
| Lymph Node Metastasis | | 46.793 | 0.000 | | 4.286 | 0.000 | | 6.706 | 0.000 |
| Yes (27 cases) | 1.01±0.08 | | | 2.24±0.60 | | | 2.13±0.53 | | |
| No (81 cases) | 0.29±0.06 | | | 1.95±0.10 | | | 1.65±0.22 | | |
| T Stage | | 10.444 | 0.000 | | 23.660 | 0.000 | | 7.378 | 0.000 |
| T2~T3 (51 cases) | 0.25±0.05 | | | 1.53±0.06 | | | 1.67±0.23 | | |
| T3~T4 (57 cases) | 0.40±0.09 | | | 1.98±0.12 | | | 2.05±0.29 | | |
| Gleason score | | 25.187 | 0.000 | | 88.918 | 0.000 | | 20.489 | 0.000 |
| ≤6 (34 cases) | 0.42±0.05 | | | 1.64±0.16 | | | 1.82±0.22 | | |
| >6 (74 cases) | 0.81±0.08 | | | 4.85±0.18 | | | 3.02±0.30 | | |

**Table 3** Comparison of Magnetic Resonance Imaging Parameters Between Two Groups

| | PCa Group (n=108) | BPH Group (n=102) | $_{x}$2/t | P |
|---|---|---|---|---|
| MRI sagittal diameter (mm) | 38.88±4.83 | 44.07±4.81 | 7.789 | 0.000 |
| MRI anteroposterior diameter (mm) | 47.19±4.48 | 52.94±4.86 | 8.925 | 0.000 |
| MRI transverse diameter (mm) | 45.01±6.47 | 46.48±5.62 | 1.750 | 0.082 |
| PI-RAD | 4.23±0.46 | 3.43±0.45 | 12.717 | 0.000 |

## Comparison of Magnetic Resonance Imaging Parameters Between Two Groups

PCa group had smaller MRI sagittal diameter and anteroposterior diameter in comparison to BPH group ($P < 0.05$), furthermore, PCa group had larger PI-RAD in comparison to BPH group ($P < 0.05$) (Table 3).

# Discussion

PCa, as one of the common malignant tumors in the male urinary system, ranks the second in the global male cancer incidence rate and the fourth in the cancer mortality rate.[22,23] Early patients often do not have specific clinical manifestations and are not easily distinguishable from benign lesions such as BPH and prostatitis.[24] Therefore, until PCa presents with urinary tract obstruction symptoms, most patients have already reached the advanced stage. Establish an effective clinical diagnostic tool for PCa and explore more and more effective PCa diagnostic markers to provide a basis for the early identification of PCa patients.

In our study, we found that STAT6 mRNA, ERG mRNA, and miR-647 expression in Pca tissues were all higher than those in BPH tissues. In the tumor microenvironment of prostate cancer, various cytokines and growth factors are secreted. These factors can activate intracellular signaling pathways, including the JAK-STAT pathway.[25] Activation of the JAK-STAT pathway may lead to upregulation of STAT6 expression. Genetic alterations or mutations in prostate cancer cells themselves may directly affect the regulation of STAT6, resulting in its increased level.[26] Additionally, the interaction between tumor cells and stromal cells in the prostate cancer microenvironment may also influence the expression and activation of STAT6.[27] Stromal cells may secrete factors that promote STAT6 activation and accumulation. Moreover, epigenetic modifications, such as DNA methylation and histone acetylation, may also play a role in regulating the expression of STAT6 in prostate cancer, either enhancing or suppressing its expression.[28] The complex

network of signaling molecules and regulatory factors within the tumor can contribute to the dysregulation of STAT6 and its consequent elevation in prostate cancer patients. Therefore, the level of STAT6 may have potential as a biomarker to assess the aggressiveness and prognosis of prostate cancer, helping in treatment decision-making.

Some studies had found that fusions between the TMPRSS2 gene and the ERG gene are frequently found in prostate cancer.[29–31] These genetic fusions can lead to dysregulated expression and overactivation of ERG, resulting in an increased level.[32] On the other hand, aberrant activation of certain signaling cascades within the tumor microenvironment may promote the upregulation of ERG.[33] For example, alterations in growth factor signaling or hormonal signaling pathways might contribute to enhanced ERG expression.[34–36] Therefore, the increase of ERG level can help in the diagnosis and identification of prostate cancer, providing valuable information for clinicians to make more accurate judgments.

In this research, the results showed that miR-647 is highly expressed In prostate cancer tissues, which was consistent with current findings.[9,10] Aberrant methylation patterns or changes in histone modifications in the genomic region of miR-647 may contribute to its increased expression.[37] Interactions with transcription factors that are abnormally activated or regulated in prostate cancer can also drive the high expression of miR-647.[38] These transcription factors may bind to specific sites on the miR-647 promoter and facilitate its transcription. In addition, the tumor microenvironment, including factors secreted by other cells or extracellular matrix components, may provide cues that stimulate miR-647 expression.[39] Meanwhile, more evidence is also needed to confirm the role and mechanism of miR-647 in prostate cancer.

Interestingly, there was no STAT6 nuclear staining in human Pca tissues. One possible reason that there are post-translational modifications or regulatory events that prevent STAT6 from translocating to the nucleus or being properly activated in prostate cancer cells. These modifications could include phosphorylation, acetylation, or other modifications that affect its function and localization. On the other hand, due to downregulation of the STAT6 gene or suppression of its expression through various epigenetic or transcriptional mechanisms, the expression level of STAT6 itself might be very low. In addition, differences in sample collection, processing, or staining techniques could potentially contribute to the lack of observed STAT6 nuclear staining. Variations in fixation, antigen retrieval, or antibody specificity might lead to false-negative results. We cannot deny that the biological complexity of prostate cancer means that not all relevant factors or markers may be easily detected or understood. There could be additional undiscovered factors or interactions that influence the absence of STAT6 nuclear staining in this context. Therefore, further research is needed to fully understand the complex mechanisms underlying the STAT6 in prostate cancer patients and its specific roles in the disease process.

Several established biomarkers, such as PCA3 and the TMPRSS2-ERG fusion, have been widely recognized and utilized in the diagnosis and prognosis of prostate cancer (PCa). PCA3, a non-coding RNA, has shown high specificity for prostate cancer detection and is used as a supplementary diagnostic tool, particularly in patients with elevated prostate-specific antigen (PSA) levels who are at risk for PCa.[40] The TMPRSS2-ERG fusion gene, another significant biomarker, is commonly observed in PCa and has been linked to disease progression and prognosis, especially in cases of early-stage cancer.[41] These biomarkers have provided valuable insights into PCa biology, leading to improved diagnostic strategies and personalized treatment options. In contrast, miR-647, STAT6, and ERG offer novel perspectives that could complement these established biomarkers. While PCA3 and TMPRSS2-ERG fusion are primarily focused on gene expression and fusion events, miR-647, a microRNA, has the potential to regulate multiple signaling pathways involved in cancer progression, offering a new layer of molecular insight. STAT6, a transcription factor, has been implicated in immune regulation and tumor microenvironment modulation, potentially influencing both tumor growth and response to therapy.[42] The ERG gene, although known for its role in gene regulation in various cancers, is still under investigation for its specific mechanisms in prostate cancer, with its dysregulation potentially contributing to tumorigenesis by promoting cell proliferation and survival.[43] By comparing these established biomarkers to miR-647, STAT6, and ERG, it becomes evident that while the latter trio may not yet be as widely used in clinical practice, their emerging role as predictive biomarkers offers substantial promise. Their involvement in different biological pathways suggests they could provide additional value for early diagnosis, prognosis prediction, and therapeutic decision-making in prostate cancer. Further research is needed to validate their clinical utility and to explore how they could be integrated with existing biomarkers to enhance patient outcomes.

However, there existed some limitations. First, the study is based on a relatively small sample size, which may limit the generalizability of the findings to the broader population. Additionally, while the expression levels of STAT6, ERG, and miR-647 show potential as biomarkers, the lack of longitudinal data restricts the ability to assess their predictive power over time. The cross-sectional design of the study also does not allow for the determination of causal relationships between these biomarkers and prostate cancer progression. Moreover, the research predominantly focuses on molecular markers without considering the clinical heterogeneity of prostate cancer patients, which could influence the biomarker's effectiveness. Further studies involving larger and more diverse cohorts, as well as a long-term follow-up, are necessary to validate the clinical utility and applicability of these biomarkers.

In conclusion, the higher level of STAT6, ERG, and miR-647 in prostate tissue are closely related to the occurrence of prostate cancer and have certain value in predicting the onset of prostate cancer.

## Disclosure

The authors report no conflicts of interest in this work.

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