The IL-4 Paradox: How an Anti-Inflammatory Cytokine Promotes Prostate Cancer Progression

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Abstract

Prostate cancer is one of the most prevalent malignancies in mern worldwide, with complex immune interactions contributing to tumor progression. In contrast, benig prostatic hyperplasia (BPH) is a non-cancerous enlargement of the prostate that dos not exhibit malignant behavior. Understanding the moluceluar differences between benign and malignant prostate condition is essential, particulary regarding immune escape mechanisms that allow cancer cells to evade the immune system. Interleukin-4 (IL-4), an anti-inflammatory cytokine, has been implicated in modulating immune responses within the Tumor Microenvironment. This study was conducted using a retrospective, observational analytical design with a cross-sectional approach to investigates the relationship between IL-4 expression and apoptosis-associated immune checkpoint receptors (PD-1, CTLA-4) and their ligand (PD-L1, PD-L2) in prostate tissue. A total of 40 formalin-fixed, paraffin-embedded (FFPE) prostate tissue samples collected between 2014 and 2020 were analyzed using quantitive real-time PCR (qRT-PCR). Samples were categorized into four groups: BPH, non-metastatic prostate cancer, metastatic prostate cancer, and controls. Statistical analysis was performed using one-way ANOVA and Pearson correlation. IL-4 expression was significantly higher in prostate cancer tissues (both metastatic and non-metastatic) compares to BPH ($p = 0.006$). Among the immune checkpoint molecules, IL-4 showed the srongest correlation with PD-L1 ($r = 0.919$), followed by PD-L2 ($r = 0.832$) and PD-1 ($r = 0.626$). In the BPH group, CTLA-4 exhibited the highest ecpression, with IL-4 ranked second. In conclusion, IL-4 expression is closely associated with key immune checkpoint markers in prostate cancer, suggesting a potential role in promoting immune escapen and tumor progression.

Keyword: Prostate Cancer, IL-4, PD-1, CTLA-4, PD-L1 and PD-L2.

INTRODUCTION

Prostate cancer is among the most frequently diagnosed malignancies in men and ranks as the second most prevalent cancer globally, following lung cancer. It has been reported in 112 countries, accounting for approximately 14.1% of all male cancer cases, with an estimated 1.41 million new diagnoses and 375,304 related deaths annually (Zhang et al., 2023). Typically, prostate cancer progresses slowly, and its development is influenced by a range of factors, including genetic predisposition, hormonal regulation, environmental exposures, and lifestyle habits. In recent years, innovative therapeutic approaches, such as immunotherapy, have emerged to enhance prostate cancer management.

The progression of prostate cancer is profoundly influenced by the tumor microenvironment (TME), which plays a pivotal role in supporting tumor cell survival, proliferation, invasion, and metastasis. A key component of the TME is the immune cell population, comprising T cells, macrophages, dendritic cells, and myeloid-derived suppressor cells (MDSCs) (Kwon et al., 2021; Messex & Liou, 2023). The immune system interacts with tumor cells in a dual capacity, both facilitating and restraining tumor development and progression. This dynamic process interplay is referred to as cancer immunoediting, a process that unfolds in three distinct phases. In the elimination phase, immunosurveillance detects and destroys malignant cells. During the equilibrium phase, immune pressure favors the selection of tumor variants with increased resistance. Ultimately, the escape phase ensues, wherein tumor cells circumvent immune control, leading to unchecked tumor growth and the clinical manifestation of cancer, a phenomenon known as immune escape (Tang et al., 2020).

A central mechanism of immune evasion in prostate cancer involves the exploitation of immune checkpoint pathways. Programmed death-1 (PD-1), also known as CD279, is a transmembrane inhibitory receptor expressed on activated T cells that plays a crucial role in regulating T cell exhaustion and apoptosis (Han et al., 2020). PD-1 binds to its ligands, PD-L1 and PD-L2, which are expressed on tumor cells, antigen-presenting cells (APCs), and other stromal components within the tumor microenvironment (TME) (Li et al., 2018; Patsoukis et al., 2020; Pauken & Wherry, 2015; Topalian et al., 2015; Zong et al., 2021). Together with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), these checkpoint molecules are frequently upregulated in prostate cancer, contributing to T cell suppression, immune escape, and resistance to immune-mediated tumor eradication (He et al., 2017; Sharma et al., 2017; Syn et al., 2017).

Interleukin-4 (IL-4) has been identified in various malignancies, including melanoma, colorectal cancer, non-Hodgkin lymphoma, gastric cancer, breast cancer, skin cancer, and bladder cancer. Its expression is notably elevated under conditions of low androgen levels and is associated with increased expression of microRNA-21 (miR-21) (Musabak et al., 2003; Ruiz-Lafuente et al., 2015). MiR-21 enhances Androgen Receptor (AR) expression in AR-negative cells through a feedback loop mechanism (Fernandes et al., 2019). Furthermore, IL-4 can activate AR by upregulating CBP/p300 expression and promoting AKT signalling interactions, thereby facilitating androgen-independent tumour growth (Lee et al., 2003, 2009; Takeshi et al., 2005). This study aims to investigate the association between IL-4 expression and apoptosis-related immune checkpoint receptors (PD-1, CTLA-4), as well as Programmed Death-1 ligands (PD-L1, PD-L2), within the prostate cancer tumour microenvironment.

METHODS

This study employed a retrospective, observational analytical design with a cross-sectional approach. Its primary objective was to examine the relationship between IL-4 expression and apoptosis-associated genes within the prostate cancer tissue microenvironment. Cluster random sampling was utilized to select participants. In this context, clusters were defined as groups of prostate cancer patients categorized by the type of clinical procedure undergone, either prostate biopsy or transurethral prostatectomy. From these clusters, samples were randomly selected to ensure equal inclusion probability across subgroups, thereby minimizing selection bias and enhancing the representativeness of the study population.

The sample comprised formalin-fixed paraffin-embedded (FFPE) prostate tissue from patients with histopathologically confirmed prostate cancer. FFPE blocks were obtained from either prostate biopsy or transurethral prostatectomy specimens. Due to the known risk of RNA degradation in FFPE tissue, quality assessment was conducted using both RNA Integrity Number (RIN) and DV200 values, which measure the proportion of RNA fragments exceeding 200 nucleotides. Samples with DV200 values below 30% or RIN scores below acceptable thresholds were excluded to minimize bias associated with degraded RNA. To further mitigate degradation, only FFPE blocks less than three years old were included. Exclusion criteria encompassed the absence of baseline Total Prostate-Specific Antigen (PSA) data, absence of baseline Total Testosterone data, FFPE block age exceeding three years, and poor RNA integrity.

Prostate biopsies and transurethral prostatectomies were performed in accordance with the guidelines and standard operating procedures of our medical centre. All experimental protocols were approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing at Universitas Gadjah Mada (Approval No. KE/FK/0109/EC/2022). Informed consent was obtained from all participants and/or their legal guardians.

RNA Extraction

The RNA genome was extracted from formalin-fixed paraffin-embedded (FFPE) prostate tissue. In FFPE tissue specimens, a deparaffinization procedure was carried out using deparaffin liquid, RNA was extracted using the Hybrid-R miRNA kit.

RT-qPCR

The RNA extraction product was examined by RT-qPCR using the Bioner Accupower Greenstar RT-qPCR Master Mix. For normalization of gene expression data, Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) was used as the endogenous housekeeping gene. The PCR was performed using Veriti Thermal Cycler under the following conditions:Reverse Transcription at 50-70^{o}C for 15 minutes followed by 1 cycle of pre-Denaturation at 95^{o}C for 5 minutes, denaturation at 95^{o}C for 30 seconds, 40 cycles Annealing/Extension/Detection at 55-60^{o}C for 30 seconds and 1 cycle of melting. The primer sequence for IL-4 is Forward CCGTAACAGACATCTTTGCTGCC and Reverse GAGTGTCCTTCTCATGGTGGCT. And The primer sequence for PD-1 Forward GACTATGGGGAGCTGGATTT, PD-1 Reverse

AGAGCAGTGTCCATCCTCAG, CLTA4 Forward GCTCTACCTCTTGAAGACCT, CLTA4 Reverse AGTCTCACTCACCTTTGCAG, PD-L1 Forward TGATACACATTTGGAGGAGACG, PD-L1 Reverse CCCTCAGGCATTTGAAAGTATC, and PD-L2 Forward GCTTCACCAGATAGCAGCTTTATTC and for PD-L1 Reverse CTCCAAGGTTCACATGACTTCCA (Danarto et al., 2021).

Statistical Analysis

Descriptive and analytical statistical analyses were performed on a total of 40 research samples. The normality of data distribution was assessed using the Shapiro-Wilk test, suitable for sample sizes less than 50. For group comparisons, the parametric ANOVA test was used for normally distributed data, while the non-parametric Kruskal-Wallis test was used for data that were not normally distributed. Correlation analysis was conducted to assess the relationship between variables, using the Pearson correlation test for parametric data and the Spearman correlation test for non-parametric data.

RESULTS

The samples taken were 40 FFPE preparations, including 12 samples diagnosed with Benign Prostate Hyperplasia (BPH), 8 samples of non-metastatic prostate cancer, and 20 samples of metastatic prostate cancer. The mean age of the patients is 68.5 years.

Table 1. Sample Characteristics

Variabel	Total	BPH	Prostate Cancer			*P*-value (normality test)
			Non-MPCa	M1b PCa	M1c PCa	
Number of patients, n (%)	40	12 (29.3)	8 (19.5)	8 (19.5)	12 (29.3)	
Mean Age, years ± SD	68.5 ± 8.3					>0.05*
Mean Expression ± SD						
IL-4 (Mean ± SD)		10.7 ± 7.7	69.7 ± 35.9	50.4 ± 28.5	63.3 ± 61.1	>0.05*
CTLA-4 (Mean ± SD)		82.5 ± 52.3	64 ± 30.8	38.5 ± 20.3	71.8 ± 30.5	>0.05*
PD-1 (Mean ± SD)		2.6 ± 0.5	4.2 ± 1.1	4.8 ± 1.1	4.3 ± 1.2	<0.05
PD-L1 (Mean ± SD)		1.5 ± 0.4	92.5 ± 56	70.9 ± 48.1	76.1 ± 87.1	>0.05*
PD-L2 (Mean ± SD)		6.9 ± 2.6	480 ± 310.9	241.7 ± 160.1	462.3 ± 588.5	>0.05*

*Normal distribution

The distribution of samples for each gene was tested using the Shapiro-Wilk test. The data distribution of the IL-4, CTLA-4, PD-L1, and PD-L2 genes cytokine were normal, but the distribution of PD-1 was not normal. In table 1, the midpoint concentration of IL-4 appears to be directly proportional to the expression of PD-L1 and PD-L2 in both BPH, Non-Metastatic

Prostate Cancer (Non-MPCa), and in Metastatic Prostate cancer (M1b PCa and M1c PCa) with p-value 0.006.

In the BPH group sample, CTLA-4 had the highest expression level, followed by the expression of IL-4, PD-L2, then PD-1 and PD-L1. However, in the third column of prostate cancer, in non-metastatic prostate cancer and metastatic prostate cancer, PD-L2 had the highest expression level, followed by PD-L1, CTLA-4, IL-4, and PD-1 with a p-value 0.012.

Table 2. Univariate Comparative Analysis

Variable	BPH	Prostate Cancer			*P*-value
		Non-MPCa	M1b PCa	M1c PCa	
IL-4 (Mean ± SD)	10.7 ± 7.7	69.7 ± 35.9	50.4 ± 28.5	63.3 ± 61.1	0.006*
CTLA-4 (Mean ± SD)	82.5 ± 52.3	64 ± 30.8	38.5 ± 20.3	71.8 ± 30.5	0.089*
PD-1 (Mean ± SD)	2.6 ± 0.5	4.2 ± 1.1	4.8 ± 1.1	4.3 ± 1.2	0.390**
PD-L1 (Mean ± SD)	1.5 ± 0.4	92.5 ± 56	70.9 ± 48.1	76.1 ± 87.1	0.004*
PD-L2 (Mean ± SD)	6.9 ± 2.6	480 ± 310.9	241.7 ± 160.1	462.3 ± 588.5	0.012*

*ANOVA test
** Kruskal-Walis Test

From Table 2 we can observe that the concentration of IL-4 in prostate cancer, both metastatic and non-metastatic, is higher than in BPH, with a p-value of 0.006. There is also a significant difference in the average concentration of PD-L1 and PD-L1 between BPH and prostate cancer, with p-values of 0.004 and 0.012 respectively. In the case of PD-1 and CLTA-4, there was no significant difference in average concentration.

Table 3. Correlation Analysis IL-4

Variable	IL-4	
	r	p-value
PD-1	0.626	0.000*
PD-L1	0.919	0.000
PD-L2	0.832	0.000
CLTA-4	0.265	0.099

*Spearman correlation test

From table 3, we can observe that between IL-4 and the three variables, the correlation between IL-4 and PD-L1 is the strongest (r=0.919), between IL-4 and PD-L2 comes the second (0.832), and between PD-1 comes the third (r=0.626). The relation between those 3 variables shows a strong correlation (r-value between 0.5-1). We can also see from table 3, IL-4 correlated significantly with PD-L1, PD-L2, and PD-1. Shown by the p-value of all three variables 0.000.

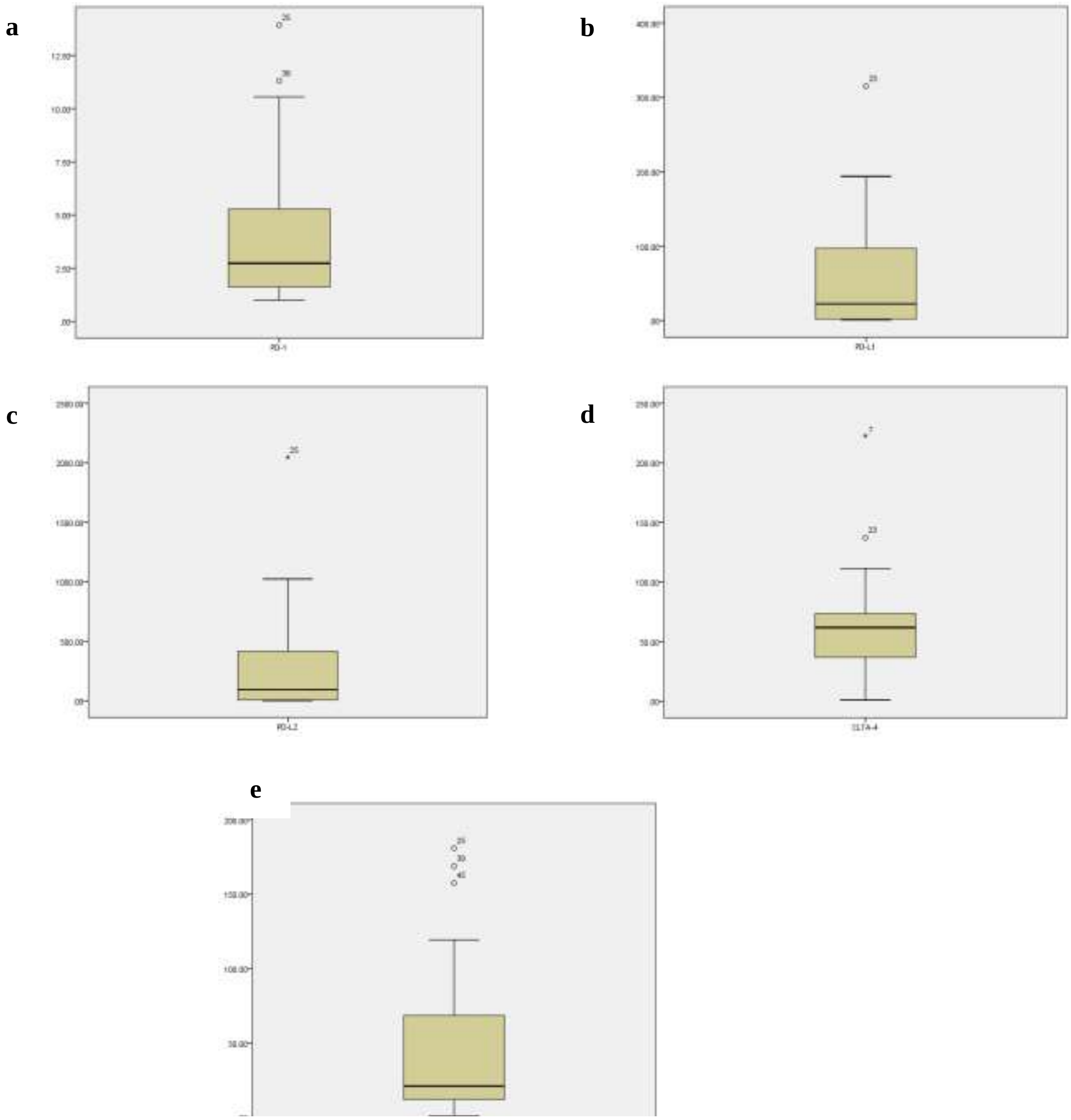

Figure 1. Boxplot of correlation between IL-4 and apoptosis-associated gene receptors (PD-1, CTLA-4) and Programmed Death-1 Ligands (PD-L1, PD-L2).

DISCUSSION

This study revealed significant associations between IL-4 expression and apoptosis-related immune checkpoint receptors (PD-1, CTLA-4), as well as Programmed Death-1 ligands (PD-L1, PD-L2), within the prostate cancer tissue microenvironment. Interleukin-4 is known to be a dominant signaling molecule in the microenvironment of Chronic Lymphocytic Leukemia (CLL)(Ruiz-Lafuente et al., 2015), and a similar pattern was observed in this study, with elevated IL-4 expression in prostate cancer tissue. Notably, IL-4 expression showed a significant correlation with PD-1 levels when comparing prostate cancer samples to those from Benign Prostatic Hyperplasia (BPH). IL-4 has also been reported in other malignancies, including melanoma, colorectal cancer, non-Hodgkin lymphoma, gastric cancer, breast cancer, skin cancer, and bladder cancer (Cottrell et al., 2019).

Programmed death-ligand 1 (PD-L1) is upregulated and expressed in various solid tumors as well as hematological malignancies. Its expression, along with that of PD-1, can be detected on the cell surface using immunohistochemistry (IHC). In this study, increased expression of both PD-1 and PD-L1 was also observed in prostate cancer tissue (Oflazoglu et al., 2004). Contrary to earlier assumptions that PD-L2 plays a minor role, recent comparative studies have demonstrated that PD-L2 is highly expressed in non-metastatic prostate cancer (non-MPCa), suggesting that its contribution to tumor progression has been underestimated. Mechanistically, PD-L2 induction is associated with Th2-driven cytokine signaling involving IL-4, IL-13, and IFN-γ, mediated through IL-4Rα and STAT6 activation in M2 macrophages (Tsirigotis et al., 2016). This immunological crosstalk underscores IL-4 as a key upstream regulator of PD-L2 expression, reinforcing its dual role in facilitating immune evasion in prostate cancer.

Immunotherapy has long been proposed as a promising approach in cancer treatment, with recent studies demonstrating its efficacy. Blocking inhibitory immune pathways such as PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) has led to notable clinical improvements in advanced melanoma, lung cancer, and kidney cancer (Tao et al., 2017). In prostate cancer, serum IL-4 levels have been shown to increase as the disease progresses. A study by Goldstein et al. reported elevated IL-4 levels during the transition to castration-resistant prostate cancer, and further noted that prognosis worsened following radical prostatectomy when IL-4 levels were significantly elevated (Goldstein et al., 2011).

Similarly, research by Takeshi et al. found that serum IL-4 levels were significantly higher in hormone-refractory prostate cancer patients compared to those with untreated prostate cancer (Takeshi et al., 2005). However, no significant differences in IL-4 levels were observed among healthy individuals, patients with benign prostatic hyperplasia (BPH), and those with untreated prostate cancer. Additionally, IL-4 levels did not vary significantly based on clinical stage, histologic grade, or Gleason score in pre-treatment patients.

Elevated levels of IL-4 receptors have been reported across various human cancers, and IL-4 may contribute directly to tumorigenesis by acting on malignant cells. Aberrant cell proliferation is a hallmark of tumor progression and a prerequisite for metastasis to distant sites. While IL-4 has been shown to exert both inhibitory and stimulatory effects on cell proliferation in general, studies involving cancer cells suggest that IL-4 predominantly promotes malignant cell proliferation, although the underlying mechanisms remain unclear. Findings from this study demonstrate that IL-4 serves as a potent inducer of PC3 prostate cancer cell proliferation under conditions of nutrient-depletion stress (Roca et al., 2012).

Elevated IL-4 levels have been observed in patients with hormone-refractory prostate cancer. Moreover, the application of recombinant IL-4 has been shown to upregulate the expression of annexin A5 and syncytin, two proteins that play critical roles in cell-cell fusion processes. Conversely, IL-4 inhibition reduces their expression and suppresses both cell proliferation and fusion. In pancreatic tumors, IL-4 of autocrine origin is essential for the transition of normal macrophages into tumor-promoting macrophages. Notably, IL-4 expression is low in normal pancreatic islets but increases by approximately 4.5-fold during the hyperplastic stage (Setrerrahmane & Xu, 2017).

Recent research highlights a significant correlation between Interleukin-4 (IL-4) and Programmed Cell Death Ligand-1 (PD-L1) expression, suggesting that IL-4 may contribute to the development of an immune escape phenotype in prostate cancer. Specifically, Prakoso et al. (Prakoso et al., 2024) demonstrate that IL-4 facilitates immune evasion mechanisms, positioning it as a key modulator within the prostate cancer tumour microenvironment, primarily through activation of signalling pathways such as the Akt cascade. However, the direct involvement of the androgen receptor in this process remains to be fully elucidated.

This study identified elevated PD-L2 expression levels, particularly in patients with non-metastatic prostate cancer, thereby challenging the conventional view of PD-L2 as a secondary focus in cancer research. These findings suggest that PD-L2 plays a significant role in prostate tumour progression and may influence future therapeutic strategies targeting immune checkpoint pathways. Elevated PD-L2 expression has been associated with unfavourable clinical outcomes, including biochemical recurrence and metastasis, reinforcing the proposition that IL-4 and PD-L2 could serve as dual biomarkers for immune resistance in prostate cancer (Prakoso et al., 2024).

While this study offers valuable initial insights, several limitations must be acknowledged, which in turn inform future research directions. First, the study was conducted at a single centre with a limited sample size per group (n = 8–12), potentially underpowering subgroup analyses and limiting the generalizability of the findings. Additionally, the use of formalin-fixed paraffin-embedded (FFPE) tissue presents inherent challenges, particularly regarding RNA degradation.

In response to these limitations, future research should advance along three key fronts. To address sample constraints, larger multicentre studies utilizing fresh tissue specimens are essential to ensure higher RNA quality and enable robust protein-level validation. Mechanistically, functional studies are needed to confirm IL-4's regulatory role in PD-L1 and PD-L2 expression, with particular emphasis on the IL-4→STAT6→PD-L1 signalling axis. Elevated IL-4 levels—especially in castration-resistant prostate cancer—may serve as a biomarker for intrinsic resistance to immune checkpoint inhibitors.

Moreover, the novel observation of PD-L2 upregulation in non-metastatic prostate cancer (non-MPCa) highlights an underexplored therapeutic target that could expand the scope of immune checkpoint blockade strategies. Integrating IL-4 and PD-L2 into clinical frameworks may enhance patient stratification and guide the development of next-generation immunotherapeutic approaches for prostate cancer.

CONCLUSIONS

The findings of this study suggest that IL-4 expression is associated with increased PD-L1 and PD-L2 expression in prostate cancer tissue, indicating a potential role for IL-4 in modulating immune evasion within the tumor microenvironment. These observed correlations support the hypothesis that IL-4 contributes to the upregulation of key immune checkpoint molecules, particularly in the context of androgen deprivation and progression to castration-resistant disease. Notably, elevated PD-L2 expression in non-metastatic prostate cancer further implicates this ligand in early immune regulatory changes that may influence disease trajectory.

To our knowledge, this is the first study in Indonesia to investigate the relationship between IL-4 expression and immune checkpoint regulation in the prostate cancer microenvironment. However, given its single-center design and limited sample size, future research should adopt a multicenter approach with a larger cohort to enhance statistical power and generalizability within the Indonesian context.

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