Clinical value of emerging peripheral blood protein biomarkers in prostate cancer (Review)

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Abstract. Prostate cancer (PCa) remains among the most common genitourinary tumors in elderly men, as PCa diagnosis and treatment remain major challenges. Liquid biopsy is a minimally invasive method that causes minor harm to patients with cancer. Peripheral blood protein biomarkers provide real-time PCa information and are easily accessible. The present review summarizes recent progress in identifying candidate peripheral blood protein biomarkers of PCa, including pentraxin-3, soluble E-cadherin, serum T-cell immunoglobulin, serum B- and T-lymphocyte attenuator, myeloid differentiation factor-2, pleiotrophin, spondin 2, filamin A, soluble urokinase plasminogen activator receptor, laminin subunit β-1, Golgi membrane protein 1, vitamin D-binding protein, tumor necrosis factor receptor superfamily member 9, activated leukocyte cell adhesion molecule and trophoblastic cell-surface antigen. Notably, the present review summarizes and discusses the clinical value of these proteins in PCa prediction, diagnosis, prognosis and drug resistance monitoring. These emerging peripheral blood protein biomarkers are promising for improving PCa stratification and management.

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Abbreviations: ABI, abiraterone; ALCAM, activated leukocyte cell adhesion molecule; AR, androgen receptor; AUC, area under the ROC curve; BCR, biochemical recurrence; BPH, benign prostatic hyperplasia; CRP, C-reactive protein; CI, confidence interval; CTCs, circulating tumor cells; ENZA, enzalutamide; FLNA, filamin A; Fuc-PSA, fucosylated PSA; GOLM1, Golgi membrane protein 1; GS, Gleason score; HVEM, herpesvirus entry mediator; HR, hazard ratio; LAMB1, laminin subunit b-1; ICK, immune-checkpoint-related; IVDs, *in vitro* diagnostics; mCRPC, metastatic castration-resistant prostate cancer; MD2, myeloid differentiation factor-2; mPCa, metastatic prostate cancer; MS, mass spectrometry; OR, odds ratio; OS, overall survival; PHI, prostate health index; PSA, prostate-specific antigen; PTX3, pentraxin-3; PTN, pleiotrophin; RNASE4, ribonuclease 4; ROC, receiver operator characteristic; sBTLA, serum B- and T-lymphocyte attenuator; SDC1, syndecan-1; sEV, small extracellular vesicle; SPON2, spondin 2; sTIM3, serum T cell immunoglobulin and mucin domain-3; suPAR, soluble urokinase plasminogen activator receptor; TNFRSF9, tumor necrosis factor receptor superfamily member 9; TROP-2, trophoblastic cell surface antigen; VDBP, vitamin D-binding protein; 25(OH)D, 25-hydroxyvitamin D

Key words: prostate cancer, peripheral blood protein biomarkers, diagnostic value, predictive value, prognostic value, drug resistance monitoring value

Contents

1. Introduction

In the US, incidence of PCa has increased annually by 2-3% between 2015 and 2019 (1). Additionally, US projections for 2024 show that prostate, lung and colorectal cancers account for almost half of all new diagnoses in men, with PCa alone accounting for up to 29% of these cases (1). Currently, available diagnostic techniques include PCa biopsy, digital rectal examination and prostate-specific antigen (PSA) testing (2). Although PSA is the most commonly used biomarker for PCa diagnosis (3), its low specificity and sensitivity often

result in misdiagnosis (4), such as in cases of elevated PSA in prostatitis and benign prostatic hyperplasia (BPH) (5). In addition, PSA-based screening may lead to overdiagnosis and increase the risk of overtreatment through the detection of indolent PCa (6,7). Therefore, there is a great demand to find biomarkers that can precisely and dynamically characterize the development and progression of PCa.

In men with an abnormal PSA level, transrectal ultrasound-guided biopsy has remained the standard procedure for PCa diagnosis (8,9). However, there is a higher rate of complications after prostate biopsy in men who are anxious about these complications (10,11). Liquid biopsy is a minimally invasive method that offers the advantage of real-time monitoring with minimal harm to patients with cancer (12,13). The development of a non-invasive 'liquid biopsy' represents a notable innovation in the field of precision medicine (14). These non-invasive detection biomarkers include DNA, circulating tumor cells, RNAs (microRNA, long non-coding RNAs and mRNAs), proteins, sugar structures, metabolites and peptides (14,15). In addition, research involving large-scale mass spectrometry-based proteomics of PCa has previously been published (16,17). An increasing number of serum protein biomarkers, such as thrombospondin-1 and cathepsin D, that are increased in PCa are being investigated (9).

The present review provides a systematic summary of the emerging peripheral blood protein biomarkers for PCa. Notably, the clinical value of these protein biomarkers in PCa prediction, diagnosis, prognosis and drug resistance monitoring is further summarized and discussed, and holds great potential and promise for improving PCa stratification management.

2. Predictive value of peripheral blood protein biomarkers in PCa

Early prediction of dynamic PCa progression is important for disease management (18). A clinically useful biomarker should have high sensitivity and specificity, as well as high positive and negative predictive values (19). In the current section, peripheral blood protein biomarkers that predict the oncogenesis, aggressiveness and metastasis of PCa are summarized.

Chronic inflammation has been reported to cause up to 20% of human cancers and has been implicated in prostate carcinogenesis through several mechanisms (20). Pentraxin-3 (PTX3) represents a pivotal element of the innate immune system involved in cancer angiogenesis and proliferation (21,22). Previously, further reports revealed that PTX3 serum levels were higher in patients with PCa compared with in those with inflammation or BPH (23). By contrast, these two groups did not differ in terms of serum PSA or C-reactive protein (CRP) levels, and there was no association between PTX3 and CRP serum levels, ruling out the possibility that elevated PTX3 levels were caused by systemic inflammation (23). These findings suggest that elevated PTX3 levels in PCa may originate from the tumor's local immune microenvironment, such as the infiltration of $CD4^+CD25^+$ regulatory T cells (Tregs) (24), rather than from systemic inflammation. This does not contradict the theory in previous studies that inflammation acts as a carcinogenic driver (20,25). In addition, receiver operating characteristic (ROC) curve analysis further confirmed the reliability of PTX3 serum levels in predicting PCa development, with a cut-off value of 3.25 ng/ml and a sensitivity and specificity of 89.3 and 88.5%, respectively (23).

Moreover, in another immune-related study, high levels of serum B- and T-lymphocyte attenuator (sBTLA) and serum T-cell immunoglobulin and mucin domain-3 (sTIM3) were associated with the risk of aggressive PCa. Specifically, the q-value (Benjamini-Hochberg correction method) of sBTLA was <0.15 using multiple comparison methods [odds ratio (OR)=2.7; 95% confidence interval (CI) 1.3-5.6; P=0.01; q=0.14] (26). Researchers have also reported that the binding of herpesvirus entry mediator (HVEM)-BTLA inhibits T-cell activation and proliferation, leading to impeded antitumor immunity (26). In both studies, immune-related proteins were found to have the potential to be predictive biomarkers for PCa, whereas sBTLA and sTIM3 predicted aggressiveness. Furthermore, a previous study revealed that soluble E-cadherin is a more effective predictor of the aggressiveness of PCa compared with PSA (27). It regulates human nanos C2HC-type zinc finger 1, which interacts with p120 catenin and induces tumor cell migration and invasion (28).

Metastatic PCa (mPCa) is most often incurable and is the main cause of mortality (29). A previous study first used genomic analysis to confirm that myeloid differentiation factor-2 (MD2) showed excellent performance in predicting the risk of tumor metastasis (30). Moreover, measurements of serum MD2 protein levels revealed that their levels were associated with the metastasis of PCa (30). Recently, a group of nine proteins was shown to be elevated in mPCa compared with localized PCa by immunohistochemistry (31). In particular, pleiotrophin (PTN) levels were increased in the serum of men in the Cambridge Prognostic Groups 5 (CPG5) group compared with those in the benign and CPG1 groups (31). In addition, researchers have discovered that PTN is a secreted growth factor with multiple functions associated with tumor growth and metastasis (32). These studies suggest that PTN and MD2 may represent novel biomarkers for the prediction of localized PCa with metastatic potential, and they are expected to support clinical decision-making and optimal health care delivery. However, PCa is a highly heterogeneous tumor whose expression patterns of molecular markers notably differ across stages. The utility of these biomarkers requires further studies to confirm their validity and generalizability.

3. Diagnostic value of peripheral blood protein biomarkers in PCa

A growing number of studies have suggested that the widespread use of PSA for PCa screening and early diagnosis improves patient outcomes and reduces mortality (33-36). Ribonuclease 4 (RNASE4), a protein biomarker that enhances the diagnostic accuracy of PSA in PCa, also promotes tumor progression by stimulating cancer cell proliferation and inducing angiogenesis (37). Using an enzyme-linked immunosorbent assay, Vanli *et al* (37) measured RNASE4 levels in plasma samples from healthy controls (n=120) and patients with PCa (n=120). The results revealed that the ROC curve of RNASE4 plus PSA provides the most accurate PCa diagnosis, with an area under the ROC curve (AUC) of 0.99

(0.98-1.00) (37), suggesting that the plasma RNASE4 level in combination with the PSA level improves diagnostic accuracy and reduces misdiagnosis.

In addition, spondin 2 (SPON2) is considered to be a promising diagnostic biomarker for PCa when the PSA concentration is <4 ng/ml (38). As members of the F-spondin family can modulate the Wnt/β-catenin signaling pathway during tumor development, SPON2, which belongs to this family, may promote cancer growth (39). Research regarding PCa suggests that characterizing SPON2 may help predict diagnosis (40). In patients with a total PSA <4 ng/ml, the diagnostic efficacy of SPON2 (AUC=0.921; 95% CI: 0.827-0.973) was significantly superior to that of total PSA (AUC=0.537; 95% CI: 0.409-0.660; P<0.001) (38). However, SPON2 has only been validated in a small study involving 286 patients with PCa (38). The lack of a multicenter cohort limits its practical applicability.

Filamin A (FLNA) is influenced by the effects of androgens on cell migration and FLNA cleavage (41). It has been identified as a potential serum biomarker for PCa diagnosis (42). Recently, the clinical value of FLNA in the diagnosis of PCa has also been researched. In men with a PSA concentration between 4 and 10 ng/ml (the gray zone) and a negative digital rectal examination, FLNA serum levels were shown to reliably distinguish patients with PCa from those with BPH (43,44). It is also worth mentioning that Golgi membrane protein 1 (GOLM1), a Golgi protein upregulated in localized PCa (45), was shown by Dong *et al* (46) to have excellent diagnostic efficacy in the PSA gray zone. The ROC curve analysis indicated that GOLM1 had a sensitivity of 0.774 and a specificity of 0.713 when the PSA concentration was within the 4-10 ng/ml range, demonstrating superior sensitivity and specificity compared with PSA (46). The research identified GOLM1 and FLNA as potential biomarkers for diagnosing PCa in the gray zone. These biomarkers may reduce the likelihood of prostate biopsy in patients. However, the diagnostic utility of these protein biomarkers still needs to be determined in larger populations before their broad clinical application.

The inability of current diagnostic tests to distinguish between indolent and aggressive PCa is a major clinical challenge (47). Soluble urokinase plasminogen activator receptor (suPAR) may indirectly induce tumor cell proliferation, migration and invasion (48). Recently, research on suPAR as a diagnostic biomarker for aggressive PCa has shown promising progress. A study by Wach *et al* (49) revealed that serum suPAR levels were higher in patients with a Gleason score (GS) >7 compared with in those with a GS 5-7 or <5 (P<0.011), supporting the clinical value of suPAR in identifying aggressive PCa. On the basis of this evidence, suPAR can be proposed as a stratified biomarker for high GS (>7) PCa.

Advanced PCa is prone to metastasis (50), and new findings on diagnostic biomarkers for mPCa have been reported in recent research (46,51). In PCa, laminin subunit b-1 (LAMB1) expression was reported to be associated with cell motility and invasion into the surrounding extracellular matrix (52), suggesting its potential utility as a metastatic biomarker. Pang *et al* (51) reported that plasma small extracellular vesicle (sEV) LAMB1 levels were higher in the PCa metastasis group compared with in the high-risk, healthy and BPH groups (P<0.0001). Furthermore, sEV LAMB1 has greater diagnostic value for PCa, and the combination of LAMB1 and PSA had an AUC value of 0.9348 (95% CI from 0.8495 to 1; P<0.0001) (51). In addition, Dong *et al* (46) reported that serum GOLM1 levels were highest in patients with metastatic PCa, and that its abundance was positively associated with progression. As a result, LAMB1 and GOLM1 should be further investigated as potential protein biomarkers to improve the diagnosis of mPCa.

Wu *et al* (53) used genetic variants associated with blood protein levels as a tool to assess the association between genetically predicted protein levels and PCa risk, an approach that reduces the bias associated with traditional epidemiological studies. A total of 13 protein biomarkers were positively associated with PCa risk, with T-cell surface protein tactile activity being the most notably positively associated with risk (OR, 1.22) (53). These findings contribute to the development of appropriate biomarker panels for the early diagnosis of PCa.

4. Prognostic value of peripheral blood protein biomarkers in PCa

As PCa is remarkably heterogeneous, it can be classified into several intermediate clinical states, and the management of the therapeutic course of the different states and the timely prevention of metastatic disease may benefit from clinically useful prognostic biomarkers (54). In the current section, circulating protein biomarkers that hold prognostic value for classifying PCa, predicting disease prognosis, overall survival (OS) and biochemical recurrence (BCR) are briefly summarized.

Strong evidence from histology and genetic studies suggests that persistent systemic inflammation may serve a role in the early stages of PCa development (55-57). Kälin *et al* (58) identified important prognostic biomarkers for PCa, including CRP, in a PTEN conditional knockout mouse model. In addition, another study revealed that serum CRP levels were associated with increased odds of high-risk PCa, mPCa and high PSA levels (≥20 mg/), with ORs of 1.29 (95% CI, 1.06-1.56), 1.32 (95% CI, 1.05-1.65) and 1.51 (95% CI, 1.26-1.81), respectively (59). Similarly, higher haptoglobin levels were associated with the likelihood of mPCa, high PSA levels and high-grade PCa (59). These studies suggest that CRP and haptoglobin levels predict poor prognosis in PCa.

In addition, Hendrickson *et al* (60) observed that elevated levels of vitamin D receptor (VDR) in PCa tissue were associated with a reduced risk of fatal cancer. Subsequently, Yuan *et al* (61) reported that the OR was 0.31 (95% CI, 0.15 to 0.65) for patients with advanced PCa with both vitamin D binding protein (VDBP) and total 25-hydroxyvitamin D [25(OH)D] levels above the mean vs. those with lower mean total 25(OH)D levels and higher mean VDBP levels. These results are consistent with the biological function of VDBP-macrophage activators in inhibiting tumor growth by suppressing cancer cell proliferation and migration (62). Therefore, VDBP may be a prognostic factor for the risk of advanced and lethal PCa.

BCR and metastatic progression in PCa were independently predicted by high tissue PTN (31). Moreover, Minas *et al* (63) examined the association between immune-related proteins, including PTN, and the risk of developing PCa in 3,094 serum samples. The study revealed that 33% of patients with

elevated levels of tumor necrosis factor receptor superfamily member 9 (TNFRSF9) and PTN succumbed to PCa within a 10-year period, whereas only 5% of patients with low levels of either protein died of PCa, supporting the ability of PTN and TNFRSF9 to predict poor prognosis and OS. Tregs expressing TNFRSF9 can suppress antitumor immune responses (64). This biological role is consistent with research findings that serum TNFRSF9 is associated with lethal PCa (63). In addition, treatment efficacy may be affected by soluble T-cell regulatory proteins [mostly immune checkpoint-related (ICK)-related proteins] released from immune and tumor cells (65). Wang *et al* (26) reported that serum levels of several ICK-related proteins were associated with PCa progression and BCR. Specifically, sCD28, sCD80, soluble cytotoxic T-lymphocyte antigen 4, soluble glucocorticoid-induced tumor necrosis factor receptor, soluble HVEM and soluble indoleamine 2,3-dioxygenase were associated with both BCR and progression risk (all $P<0.05$) (26). Moreover, among the ICK factors, sBTLA was the most important serum biomarker associated with progression ($P=3.3x10^{-3}$; q=0.028; HR=6.5; 95% CI, 1.9-22.8) (26). Management of PCa requires refinement and standardization, and these emerging serum biomarkers can improve PCa risk stratification and prediction of BCR. However, further studies are needed to confirm the association of the tumor immune suppression signature with PCa.

5. Value of drug resistance monitoring of peripheral blood protein biomarkers in patients with PCa

In the past decade, PCa management has notably changed. In addition to surgical treatment and chemotherapy, novel drug treatments, such as cabazitaxel (66), next-generation androgen receptor (AR) inhibitors, abiraterone (ABI) (67), enzalutamide (ENZA) (68), immunotherapy (sipuleucel-T) (69) and poly ADP-ribose polymerase inhibitors (70), have become available. However, the outcome remains poor for men who progress to metastatic castration-resistant prostate cancer (mCRPC) (71). Improved drug resistance monitoring strategies are still urgently needed.

Ryan *et al* (72) reported that serum androgens are prognostic biomarkers of OS in patients with mCRPC. Adding the AR inhibitor darolutamide to ADT and docetaxel significantly improved OS vs. placebo, confirming that suppression of androgen led to a clinical benefit (73). After persistent efforts, patients with mCRPC now have access to novel therapies, such as next-generation AR inhibitors [ABI (67) and ENZA (68)]. Recently, a study by Csizmarik *et al* (74) identified activated leukocyte cell adhesion molecule (ALCAM) as a potential biomarker for monitoring ABI and ENZA resistance. In the ENZA cohort, ALCAM serum levels significantly increased with increasing baseline PSA, lactate dehydrogenase, alkaline phosphatase and CRP levels (all $P<0.05$) (74). In the ABI cohort, ALCAM levels were higher in patients with pain ($P=0.013$) and higher PSA, alkaline phosphatase and lactate dehydrogenase levels compared with baseline ($P<0.05$) (74). Furthermore, multivariable analysis revealed high PSA and ALCAM (<131.9 ng/ml) levels as independent predictors of OS ($P=0.041$ and $P=0.002$, respectively) (74). Moreover, small interfering RNA-mediated knockdown of ALCAM resulted in its silencing, markedly increasing sensitivity to ENZA (74). The limitations of the study include that it only used mCRPC samples and did not explore the value of serum ALCAM in other stages of drug resistance, such as androgen dependence and castration resistance (75).

In addition, trophoblastic cell-surface antigen (TROP-2) is a transmembrane protein that is expressed in PCa and is overexpressed in multiple malignancies (76-78). It is a therapeutic target for antibody-drug conjugates (79) and captures peripheral blood circulating tumor cells (CTCs) in mCRPC (80). The results indicated that the number of CTCs captured with anti-TROP-2 antibodies was strongly associated with the number of CTCs captured with epithelial cell adhesion molecule antibodies (Pearson r=0.92) (80). By monitoring the number of TROP-2-positive CTCs, the response of a patient to treatment and disease progression can be assessed (80). The TROP-2 gene is expressed in mCRPC from luminal and basal tumors but is expressed at lower levels in patients with neuroendocrine PCa (80). ALCAM and TROP-2 can be used as biomarkers for further research, to monitor the effect of treatment in real time, assess dynamic changes in mCRPC and provide a basis for personalized treatment. The aforementioned protein markers are summarized in Table I with their associated clinical values.

6. Limitations and future directions

In accordance with the evidence presented in the current review, several questions remain to be addressed: i) The capacity to fulfill the identical rigorous enrollment requirements stipulated in the clinical trial study design; ii) the potential for these peripheral blood protein biomarkers to be used in clinical applications; iii) the impact of multiple treatment methods at the same time on the accuracy of serum protein markers in clinical applications; and iv) the potential benefits of combined testing for patients.

As previously discussed, the emerging peripheral blood protein biomarkers for PCa are discussed in the present review, and their clinical value and potential applications are highlighted. However, a biomarker should undergo five major phases of development before it is utilized in clinical settings to benefit the population. These phases include: i) Preclinical exploratory studies; ii) clinical assay development and validation; iii) retrospective longitudinal studies; iv) prospective screening studies; and v) randomized control studies (81). Most biomarkers discussed in the present review have completed the first two phases (preclinical exploration and assay validation), providing a strong foundation for further investigation. Regrettably, these protein biomarkers have not yet undergone a complete cycle of development. For example, LAMB1 has not been subjected to long-term monitoring or randomized control studies. In the absence of randomized testing in the general population, determining whether LAMB1 can reduce the overall disease burden is not possible. Ferrari *et al* (30) validated the importance of MD2 for predicting metastasis in a murine model but lacked prospective screening studies and multicenter cohorts. The absence of these stages makes it impossible to determine the optimal timing of the test and complicates the screening of the target population, consequently increasing the risk in clinical trials. Moreover, these protein biomarkers require higher-level clinical validation,

Table I. Peripheral blood protein biomarkers for prostate cancer and clinical value.

Protein	Proteomic technology	Clinical value	(Refs.)
PTX3	ELISA	Predictive marker	(21-23)
TIM-3	ELISA	Predictive marker	(26)
E-cadherin	ELISA	Predictive marker	(27)
MD2	IHC	Predictive marker	(30)
BTLA	ELISA	Predictive/prognostic marker	(26)
PTN	Olink proteomics planes, IHC, ELISA	Predictive/prognostic marker	(31,63)
RNASE4	LC-MS/MS	Diagnostic marker	(37)
SPON2	ELISA, IHC	Diagnostic marker	(38,40)
FLNA	LC-MS/MS	Diagnostic marker	(43)
GOLM1	ELISA	Diagnostic marker	(46)
suPAR	ELISA	Diagnostic marker	(49)
LAMB1	LC-MS/MS, WB, ELISA	Diagnostic marker	(51)
CRP	Immunoturbidimetric method	Prognostic marker	(58,59)
Haptoglobin	Immunoturbidimetric method	Prognostic marker	(59)
VDBP	ELISA	Prognostic marker	(61)
TNFRSF9	Olink proteomics planes, ELISA	Prognostic marker	(63)
ALCAM	LC-MS/MS, ELISA	Drug resistance monitoring	(74)
TROP-2	Immunofluorescent staining	Drug resistance monitoring/therapeutic target	(80)

IHC, immunohistochemistry; WB, western blotting; LC, liquid chromatography; MS, mass spectrometry; ELISA, enzyme-linked immunosorbent assay; PTX3, pentraxin-3; TIM-3, T-cell immunoglobulin and mucin domain-3; MD2, myeloid differentiation factor-2; BTLA, B and T lymphocyte attenuator; PTN, pleiotrophin; RNASE4, ribonuclease 4; SPON2, spondin 2; FLNA, filamin A; GOLM1, Golgi membrane protein 1; suPAR, soluble urokinase plasminogen activator receptor; LAMB1, laminin subunit b-1; CRP, C-reactive protein; VDBP, vitamin D-binding protein; TNFRSF9, tumor necrosis factor receptor superfamily member 9; TROP-2, trophoblastic cell-surface antigen; ALCAM, activated leukocyte cell adhesion molecule.

such as phase III clinical trials. The results of the validation and evaluation of these peripheral blood protein biomarkers are submitted to regulatory authorities. None of the biomarkers discussed in the present review have undergone this step and therefore cannot be legally used in the clinic, which could have implications for medical decision-making and patient care or even more serious consequences.

Furthermore, current protein biomarker research requires multi-omics studies in combination with proteomics. Technological advances in mass spectrometry (MS)-based proteomics have led to high-throughput and highly sensitive analytical platforms. Sun *et al* (82) employed data-independent acquisition MS (DIA-MS) to perform comprehensive proteomic analysis on 918 tissue samples from 306 Chinese patients with PCa, identifying >10,000 distinct proteins. Moreover, the authors developed a 16-protein panel that effectively predicts BCR for patients with PCa (82). With unprecedented depth and accuracy, sample analysis has opened up new avenues for biological research and clinical applications (83). However, *in vitro* diagnostics (IVDs) require stringent quality control measures (83). Currently, most MS-based experiments are performed in research laboratories rather than IVD-certified clinical ones (83). Non-standard laboratories may lead to inconsistencies in standards. Standardizing experimental protocols and data formats would enhance reproducibility and cross-study comparisons, ultimately accelerating scientific progress (83). Moreover, methods have now been developed to detect programmed death ligand 1 expression in CTCs, and its prognostic and predictive value is currently under investigation (13). We hypothesize that technological advances will resolve a number of the challenges associated with applying these peripheral blood protein biomarkers in clinical practice such as multi-omics integration, standardization of testing and cost.

Combined tests facilitate early detection of PCa, decrease over-detection and provide information for risk stratification (84). Compared with PSA, FLNA combined with prostate volume and age in men whose PSA concentration was elevated (between 4 and 10 ng/ml) resulted in superior detection performance (43). Furthermore, logistic regression was used to identify two biomarker panels that achieved the best performance: i) Prostate health index (PHI), fucosylated PSA (Fuc-PSA), syndecan-1 (SDC1), and growth differentiation factor 15; and ii) PHI, Fuc-PSA, SDC1, and TEK receptor tyrosine kinase (85). At a fixed sensitivity of 95%, the panels demonstrated a significant improvement in specificity in the distinction between aggressive PCa and low-risk PCa (76.0 vs. 56%; P=0.029) and between low-risk PCa and non-PCa (78.2 vs. 65.5%; P=0.010) (85). Multivariate panels of serum biomarkers demonstrated improvement over the performance of the PHI, which may contribute to the management of PCa. These panels demonstrate superior performance in identifying invasive diseases, partly due to their ability to detect immune evasion. For instance, the biological function

of TNFRSF9-expressing Tregs is mediated by its soluble isoform, which is generated through alternative splicing and acts as a decoy receptor to antagonize antitumor immunity and promote tumor survival (86). Additionally, PTN promotes cancer progression through increased vascular endothelial growth factor deposition in the vasculature, leading to vascular disruption (32). The clinical relevance of these mechanisms is underscored by findings that serum levels of both TNFRSF9 and PTN are associated with lethal PCa and predict poor patient survival (63). However, the underlying relationships between them have yet to be described. The individual biomarkers referenced in the present review possess unique mechanisms of action that serve their specific clinical applications. Future mechanistic research should elucidate how these biomarkers act synergistically, thereby strengthening the link between biomarker mechanisms and specific clinical applications.

7. Conclusions

In summary, PSA is widely used in PCa testing. However, controversy exists regarding PSA screening and the risk associated with PCa overdiagnosis. Therefore, the present review summarizes the emerging peripheral blood protein biomarkers for the accurate diagnosis and selection of optimal treatment options. However, it is not currently appropriate to clinically implement the biomarkers discussed in the present review. Future efforts must prioritize higher-level validation, develop multi-omics integration strategies and forge stronger links between biomarker mechanisms and specific clinical applications. The rapidly evolving field of targeted proteomics will be instrumental in building the validation platforms needed to achieve these goals.

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Availability of data and materials

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Authors' contributions

MC wrote and completed the manuscript and abstract. FW made substantive revisions to the key content of the manuscript. WW and KF consulted the relevant literature and completed the English revisions. MC, KX and XG completed the design of the framework of the manuscript and completed the tables. WL and ZT provided constructive feedback and guidance, completed critical revisions and proofread the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Giaquinto AN and Jemal A: Cancer statistics, 2024. CA Cancer J Clin 74: 12-49, 2024.
2. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, Eberli D, De Meerleer G, De Santis M, Farolfi A, *et al*: EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate Cancer-2024 update. Part I: Screening, diagnosis, and local treatment with curative intent. Eur Urol 86: 148-163, 2024.
3. Van Poppel H, Roobol MJ, Chapple CR, Catto JWF, N'Dow J, Sønksen J, Stenzl A and Wirth M: Prostate-specific antigen testing as part of a Risk-adapted early detection strategy for prostate cancer: European association of urology position and recommendations for 2021. Eur Urol 80: 703-711, 2021.
4. Van Poppel H, Albreht T, Basu P, Hogenhout R, Collen S and Roobol M: Serum PSA-based early detection of prostate cancer in Europe and globally: Past, present and future. Nat Rev Urol 19: 562-572, 2022.
5. Usman A: Nanoparticle enhanced optical biosensing technologies for prostate specific antigen biomarker detection. IEEE Rev Biomed Eng 15: 122-137, 2022.
6. Leenen RCA, Venderbos LDF, Helleman J, Gómez Rivas J, Vynckier P, Annemans L, Chloupková R, Májek O, Briers E, Vasilyeva V, *et al*: Prostate cancer early detection in the european union and UK. Eur Urol 87: 326-339, 2024.
7. Ilic D, Djulbegovic M, Jung JH, Hwang EC, Zhou Q, Cleves A, Agoritsas T and Dahm P: Prostate cancer screening with prostate-specific antigen (PSA) test: A systematic review and meta-analysis. BMJ 362: k3519, 2018.
8. Pang B, Zhu Y, Ni J, Thompson J, Malouf D, Bucci J, Graham P and Li Y: Extracellular vesicles: The next generation of biomarkers for liquid Biopsy-based prostate cancer diagnosis. Theranostics 10: 2309-2326, 2020.
9. Lomas DJ and Ahmed HU: All change in the prostate cancer diagnostic pathway. Nat Rev Clin Oncol 17: 372-381, 2020.
10. Wade J, Rosario DJ, Macefield RC, Avery KN, Salter CE, Goodwin ML, Blazeby JM, Lane JA, Metcalfe C, Neal DE, *et al*: Psychological impact of prostate biopsy: Physical symptoms, anxiety, and depression. J Clin Oncol 31: 4235-4241, 2013.
11. Gershman B, Van Houten HK, Herrin J, Moreira DM, Kim SP, Shah ND and Karnes RJ: Impact of Prostate-specific antigen (PSA) screening trials and revised PSA screening guidelines on rates of prostate biopsy and postbiopsy complications. Eur Urol 71: 55-65, 2017.
12. Pantel K and Alix-Panabières C: Liquid biopsy and minimal residual Disease-latest advances and implications for cure. Nat Rev Clin Oncol 16: 409-424, 2019.
13. Kilgour E, Rothwell DG, Brady G and Dive C: Liquid Biopsy-based biomarkers of treatment response and resistance. Cancer Cell 37: 485-495, 2020.
14. Di Meo A, Bartlett J, Cheng Y, Pasic MD and Yousef GM: Liquid biopsy: A step forward towards precision medicine in urologic malignancies. Mol Cancer 16: 80, 2017.
15. Yu W, Hurley J, Roberts D, Chakrabortty SK, Enderle D, Noerholm M, Breakefield XO and Skog JK: Exosome-based liquid biopsies in cancer: Opportunities and challenges. Ann Oncol 32: 466-477, 2021.
16. Intasqui P, Bertolla RP and Sadi MV: Prostate cancer proteomics: Clinically useful protein biomarkers and future perspectives. Expert Rev Proteomics 15: 65-79, 2018.

17. Zhong Q, Sun R, Aref AT, Noor Z, Anees A, Zhu Y, Lucas N, Poulos RC, Lyu M, Zhu T, *et al*: Proteomic-based stratification of intermediate-risk prostate cancer patients. Life Sci Alliance 7: e202302146, 2023.
18. Pinsky PF and Parnes H: Screening for prostate cancer. N Engl J Med 388: 1405-1414, 2023.
19. Prensner JR, Rubin MA, Wei JT and Chinnaiyan AM: Beyond PSA: The next generation of prostate cancer biomarkers. Sci Transl Med 4: 127rv123, 2012.
20. De Marzo AM, Platz EA, Sutcliffe S, Xu J, Grönberg H, Drake CG, Nakai Y, Isaacs WB and Nelson WG: Inflammation in prostate carcinogenesis. Nat Rev Cancer 7: 256-269, 2007.
21. Bonavita E, Gentile S, Rubino M, Maina V, Papait R, Kunderfranco P, Greco C, Feruglio F, Molgora M, Laface I, *et al*: PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. Cell 160: 700-714, 2015.
22. Gupta G, Mou Z, Jia P, Sharma R, Zayats R, Viana SM, Shan L, Barral A, Boaventura VS, Murooka TT, *et al*: The long pentraxin 3 (PTX3) suppresses immunity to cutaneous leishmaniasis by regulating CD4+ T helper cell response. Cell Rep 33: 108513, 2020.
23. Stallone G, Cormio L, Netti GS, Infante B, Selvaggio O, Fino GD, Ranieri E, Bruno F, Prattichizzo C, Sanguedolce F, *et al*: Pentraxin 3: A novel biomarker for predicting progression from prostatic inflammation to prostate cancer. Cancer Res 74: 4230-4238, 2014.
24. Miller AM, Lundberg K, Ozenci V, Banham AH, Hellström M, Egevad L and Pisa P: CD4+CD25high T cells are enriched in the tumor and peripheral blood of prostate cancer patients. J Immunol 177: 7398-7405, 2006.
25. de Bono JS, Guo C, Gurel B, De Marzo AM, Sfanos KS, Mani RS, Gil J, Drake CG and Alimonti A: Prostate carcinogenesis: Inflammatory storms. Nat Rev Cancer 20: 455-469, 2020.
26. Wang Q, Ye Y, Yu H, Lin SH, Tu H, Liang D, Chang DW, Huang M and Wu X: Immune checkpoint-related serum proteins and genetic variants predict outcomes of localized prostate cancer, a cohort study. Cancer Immunol Immunother 70: 701-712, 2021.
27. Tsaur I, Thurn K, Juengel E, Gust KM, Borgmann H, Mager R, Bartsch G, Oppermann E, Ackermann H, Nelson K, *et al*: sE-cadherin serves as a diagnostic and predictive parameter in prostate cancer patients. J Exp Clin Cancer Res 34: 43, 2015.
28. Strumane K, Bonnomet A, Stove C, Vandenbroucke R, Nawrocki-Raby B, Bruyneel E, Mareel M, Birembaut P, Berx G and van Roy F: E-cadherin regulates human Nanos1, which interacts with p120ctn and induces tumor cell migration and invasion. Cancer Res 66: 10007-10015, 2006.
29. Gong J, Kim DM, De Hoedt AM, Bhowmick N, Figlin R, Kim HL, Sandler H, Theodorescu D, Posadas E and Freedland SJ: Disparities with systemic therapies for black men having advanced prostate cancer: Where Do We Stand? J Clin Oncol 42: 228-236, 2024.
30. Ferrari MG, Jimenez-Uribe AP, Wang L, Hoeppner LH, Murugan P, Hahm E, Yu J, Kuzel TM, Gradilone SA and Mansini AP: Myeloid differentiation factor-2/LY96, a potential predictive biomarker of metastasis and poor outcomes in prostate cancer: Clinical implications as a potential therapeutic target. Oncogene 43: 484-494, 2024.
31. Liu S, Shen M, Hsu EC, Zhang CA, Garcia-Marques F, Nolley R, Koul K, Rice MA, Aslan M, Pitteri SJ, *et al*: Discovery of PTN as a serum-based biomarker of pro-metastatic prostate cancer. Br J Cancer 124: 896-900, 2021.
32. Bai PS, Xia N, Sun H and Kong Y: Pleiotrophin, a target of miR-384, promotes proliferation, metastasis and lipogenesis in HBV-related hepatocellular carcinoma. J Cell Mol Med 21: 3023-3043, 2017.
33. de V II, Meertens A, Hogenhout R, Remmers S and Roobol MJ; ERSPC Rotterdam Study Group: A detailed evaluation of the effect of Prostate-specific Antigen-based screening on morbidity and mortality of prostate cancer: 21-year Follow-up results of the rotterdam section of the european randomised study of screening for prostate cancer. Eur Urol 84: 426-434, 2023.
34. Vynckier P, Annemans L, Raes S, Amrouch C, Lindgren P, Májek O, Beyer K, Leenen RCA, Venderbos LDF, Denijs F, *et al*: Systematic review on the cost effectiveness of prostate cancer screening in europe. Eur Urol 86: 400-408, 2024.
35. Hugosson J, Roobol MJ, Månsson M, Tammela TLJ, Zappa M, Nelen V, Kwiatkowski M, Lujan M, Carlsson SV, Talala KM, *et al*: A 16-yr Follow-up of the european randomized study of screening for prostate cancer. Eur Urol 76: 43-51, 2019.
36. de Koning HJ, Gulati R, Moss SM, Hugosson J, Pinsky PF, Berg CD, Auvinen A, Andriole GL, Roobol MJ, Crawford ED, *et al*: The efficacy of prostate-specific antigen screening: Impact of key components in the ERSPC and PLCO trials. Cancer 124: 1197-1206, 2018.
37. Vanli N, Sheng J, Li S, Xu Z and Hu GF: Ribonuclease 4 is associated with aggressiveness and progression of prostate cancer. Commun Biol 5: 625, 2022.
38. Lucarelli G, Rutigliano M, Bettocchi C, Palazzo S, Vavallo A, Galleggiante V, Trabucco S, Di Clemente D, Selvaggi FP, Battaglia M and Ditonno P: Spondin-2, a secreted extracellular matrix protein, is a novel diagnostic biomarker for prostate cancer. J Urol 190: 2271-2277, 2013.
39. Kim KA, Wagle M, Tran K, Zhan X, Dixon MA, Liu S, Gros D, Korver W, Yonkovich S, Tomasevic N, *et al*: R-Spondin family members regulate the Wnt pathway by a common mechanism. Mol Biol Cell 19: 2588-2596, 2008.
40. Qian X, Li C, Pang B, Xue M, Wang J and Zhou J: Spondin-2 (SPON2), a more prostate-cancer-specific diagnostic biomarker. PLoS One 7: e37225, 2012.
41. Mooso BA, Vinall RL, Tepper CG, Savoy RM, Cheung JP, Singh S, Siddiqui S, Wang Y, Bedolla RG and Martinez A: Enhancing the effectiveness of androgen deprivation in prostate cancer by inducing Filamin A nuclear localization. Endocr Relat Cancer 19: 759-777, 2012.
42. Di Donato M, Zamagni A, Galasso G, Di Zazzo E, Giovannelli P, Barone MV, Zanoni M, Gunelli R, Costantini M, Auricchio F, *et al*: The androgen receptor/filamin A complex as a target in prostate cancer microenvironment. Cell Death Dis 12: 127, 2021.
43. Mahaveer Chand N, Tekumalla PK, Rosenberg MT, Dobi A, Ali A, Miller GM, Aristizabal-Henao JJ, Granger E, Freedland SJ, Kellogg MD, *et al*: Filamin A is a prognostic serum biomarker for differentiating benign prostatic hyperplasia from prostate cancer in caucasian and african american men. Cancers (Basel) 16: 712, 2024.
44. Kiebish MA, Tekumalla P, Ravipaty S, Dobi A, Srivastava S, Wu W, Patil S, Friss T, Klotz A, Srinivasan A, *et al*: Clinical utility of a serum biomarker panel in distinguishing prostate cancer from benign prostate hyperplasia. Sci Rep 11: 15052, 2021.
45. Varambally S, Laxman B, Mehra R, Cao Q, Dhanasekaran SM, Tomlins SA, Granger J, Vellaichamy A, Sreekumar A, Yu J, *et al*: Golgi protein GOLM1 is a tissue and urine biomarker of prostate cancer. Neoplasia 10: 1285-1294, 2008.
46. Dong B, Xu JY, Huang Y, Guo J, Dong Q, Wang Y, Li N, Liu Q, Zhang M, Pan Q, *et al*: Integrative proteogenomic profiling of high-risk prostate cancer samples from Chinese patients indicates metabolic vulnerabilities and diagnostic biomarkers. Nat Cancer 5: 1427-1447, 2024.
47. Peng Z, Wang Y, Wu X, Yang S, Du X, Xu X, Hu C, Liu W, Zhu Y, Dong B, *et al*: Identifying high gleason score prostate cancer by prostate fluid metabolic Fingerprint-based Multi-modal recognition. Small Methods 8: e2301684, 2024.
48. Mekkawy AH, Pourgholami MH and Morris DL: Involvement of Urokinase-type plasminogen activator system in cancer: An overview. Med Res Rev 34: 918-956, 2014.
49. Wach S, Al-Janabi O, Weigelt K, Fischer K, Greither T, Marcou M, Theil G, Nolte E, Holzhausen HJ, Stöhr R, *et al*: The combined serum levels of miR-375 and urokinase plasminogen activator receptor are suggested as diagnostic and prognostic biomarkers in prostate cancer. Int J Cancer 137: 1406-1416, 2015.
50. Furesi G, Rauner M and Hofbauer LC: Emerging players in prostate Cancer-bone niche communication. Trends Cancer 7: 112-121, 2021.
51. Pang B, Wang Q, Chen H, Liu Z, Han M, Gong J, Yue L, Ding X, Wang S, Yan Z, *et al*: Proteomic identification of small extracellular vesicle proteins LAMB1 and histone H4 for prostate cancer diagnosis and risk stratification. Adv Sci (Weinh) 11: e2402509, 2024.
52. Peng Y, Wu D, Li F, Zhang P, Feng Y and He A: Identification of key biomarkers associated with cell adhesion in multiple myeloma by integrated bioinformatics analysis. Cancer Cell Int 20: 262, 2020.
53. Wu L, Shu X, Bao J, Guo X, Kote-Jarai Z, Haiman CA, Eeles RA and Zheng W; PRACTICAL, CRUK, BPC3, CAPS, PEGASUS Consortia: Analysis of over 140,000 european descendants identifies genetically predicted blood protein biomarkers associated with prostate cancer risk. Cancer Res 79: 4592-4598, 2019.

54. Adamaki M and Zoumpourlis V: Prostate cancer biomarkers: From diagnosis to prognosis and precision-guided therapeutics. Pharmacol Ther 228: 107932, 2021.
55. Sfanos KS, Yegnasubramanian S, Nelson WG and De Marzo AM: The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol 15: 11-24, 2018.
56. McMillan DC: The systemic inflammation-based glasgow prognostic score: A decade of experience in patients with cancer. Cancer Treat Rev 39: 534-540, 2013.
57. Diakos CI, Charles KA, McMillan DC and Clarke SJ: Cancer-related inflammation and treatment effectiveness. Lancet Oncol 15: e493-503, 2014.
58. Kalin M, Cima I, Schiess R, Fankhauser N, Powles T, Wild P, Templeton A, Cerny T, Aebersold R, Krek W and Gillessen S: Novel prognostic markers in the serum of patients with castration-resistant prostate cancer derived from quantitative analysis of the pten conditional knockout mouse proteome. Eur Urol 60: 1235-1243, 2011.
59. Arthur R, Williams R, Garmo H, Holmberg L, Stattin P, Malmström H, Lambe M, Hammar N, Walldius G, Robinsson D, *et al*: Serum inflammatory markers in relation to prostate cancer severity and death in the Swedish AMORIS study. Int J Cancer 142: 2254-2262, 2018.
60. Hendrickson WK, Flavin R, Kasperzyk JL, Fiorentino M, Fang F, Lis R, Fiore C, Penney KL, Ma J, Kantoff PW, *et al*: Vitamin D receptor protein expression in tumor tissue and prostate cancer progression. J Clin Oncol 29: 2378-2385, 2011.
61. Yuan C, Shui IM, Wilson KM, Stampfer MJ, Mucci LA and Giovannucci EL: Circulating 25-hydroxyvitamin D, vitamin D binding protein and risk of advanced and lethal prostate cancer. Int J Cancer 144: 2401-2407, 2019.
62. Gregory KJ, Zhao B, Bielenberg DR, Dridi S, Wu J, Jiang W, Huang B, Pirie-Shepherd S and Fannon M: Vitamin D binding protein-macrophage activating factor directly inhibits proliferation, migration, and uPAR expression of prostate cancer cells. PLoS One 5: e13428, 2010.
63. Minas TZ, Candia J, Dorsey TH, Baker F, Tang W, Kiely M, Smith CJ, Zhang AL, Jordan SV, Obadi OM, *et al*: Serum proteomics links suppression of tumor immunity to ancestry and lethal prostate cancer. Nat Commun 13: 1759, 2022.
64. Freeman ZT, Nirschl TR, Hovelson DH, Johnston RJ, Engelhardt JJ, Selby MJ, Kochel CM, Lan RY, Zhai J, Ghasemzadeh A, *et al*: A conserved intratumoral regulatory T cell signature identifies 4-1BB as a pan-cancer target. J Clin Invest 130: 1405-1416, 2020.
65. Chen Y, Wang Q, Shi B, Xu P, Hu Z, Bai L and Zhang X: Development of a sandwich ELISA for evaluating soluble PD-L1 (CD274) in human sera of different ages as well as supernatants of PD-L1+ cell lines. Cytokine 56: 231-238, 2011.
66. Beer TM, Hotte SJ, Saad F, Alekseev B, Matveev V, Fléchon A, Gravis G, Joly F, Chi KN, Malik Z, *et al*: Custirsen (OGX-011) combined with cabazitaxel and prednisone versus cabazitaxel and prednisone alone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel (AFFINITY): A randomised, open-label, international, phase 3 trial. Lancet Oncol 18: 1532-1542, 2017.
67. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PF, Sternberg CN, Miller K, Logothetis CJ, Shore ND, Small EJ, *et al*: Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 16: 152-160, 2015.
68. Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, Parker CC, Gillessen S, Cook A, Brawley C, Amos CL, *et al*: Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: A meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. Lancet 399: 447-460, 2022.
69. Rathi N, McFarland TR, Nussenzveig R, Agarwal N and Swami U: Evolving role of immunotherapy in metastatic castration refractory prostate cancer. Drugs 81: 191-206, 2021.
70. Abida W, Patnaik A, Campbell D, Shapiro J, Bryce AH, McDermott R, Sautois B, Vogelzang NJ, Bambury RM, Voog E, *et al*: Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol 38: 3763-3772, 2020.
71. Hussain M, Fizazi K, Shore ND, Heidegger I, Smith MR, Tombal B and Saad F: Metastatic hormone-sensitive prostate cancer and combination treatment outcomes: A review. JAMA Oncol 10: 807-820, 2024.
72. Ryan CJ, Molina A, Li J, Kheoh T, Small EJ, Haqq CM, Grant RP, de Bono JS and Scher HI: Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: Results from an analysis of a randomized phase III trial. J Clin Oncol 31: 2791-2798, 2013.
73. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, Kopyltsov E, Park CH, Alekseev B, Montesa-Pino Á, *et al*: Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med 386: 1132-1142, 2022.
74. Csizmarik A, Keresztes D, Nagy N, Bracht T, Sitek B, Witzke K, Puhr M, Tornyi I, Lázár J, Takács L, *et al*: Proteome profiling of enzalutamide-resistant cell lines and serum analysis identified ALCAM as marker of resistance in castration-resistant prostate cancer. Int J Cancer 151: 1405-1419, 2022.
75. Chen YM, Chen L, Xu YX, Cheng HB and Zhou JL: Shared mechanisms for metastasis and drug resistance in prostate cancer. Biochim Biophys Acta Rev Cancer 1880: 189358, 2025.
76. Cardillo TM, Govindan SV, Sharkey RM, Trisal P and Goldenberg DM: Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: Preclinical studies in human cancer xenograft models and monkeys. Clin Cancer Res 17: 3157-3169, 2011.
77. Trerotola M, Cantanelli P, Guerra E, Tripaldi R, Aloisi AL, Bonasera V, Lattanzio R, de Lange R, Weidle UH, Piantelli M and Alberti S: Upregulation of Trop-2 quantitatively stimulates human cancer growth. Oncogene 32: 222-233, 2013.
78. Tong Y, Fan X, Liu H and Liang T: Advances in Trop-2 targeted antibody-drug conjugates for breast cancer: Mechanisms, clinical applications, and future directions. Front Immunol 15: 1495675, 2024.
79. Liu X, Deng J, Yuan Y, Chen W, Sun W, Wang Y, Huang H, Liang B, Ming T, Wen J, *et al*: Advances in Trop2-targeted therapy: Novel agents and opportunities beyond breast cancer. Pharmacol Ther 239: 108296, 2022.
80. Sperger JM, Helzer KT, Stahlfeld CN, Jiang D, Singh A, Kaufmann KR, Niles DJ, Heninger E, Rydzewski NR, Wang L, *et al*: Expression and therapeutic targeting of TROP-2 in Treatment-resistant prostate cancer. Clin Cancer Res 29: 2324-2335, 2023.
81. Kim Y and Kislinger T: Novel approaches for the identification of biomarkers of aggressive prostate cancer. Genome Med 5: 56, 2013.
82. Sun R, A J, Yu H, Wang Y, He M, Tan L, Cheng H, Zhang J, Wang Y, Sun X, *et al*: Proteomic landscape profiling of primary prostate cancer reveals a 16-protein panel for prognosis prediction. Cell Rep Med 5: 101679, 2024.
83. Guo T, Steen JA and Mann M: Mass-spectrometry-based proteomics: From single cells to clinical applications. Nature 638: 901-911, 2025.
84. Nordström T, Discacciati A, Bergman M, Clements M, Aly M, Annerstedt M, Glaessgen A, Carlsson S, Jäderling F, Eklund M, *et al*: Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): A prospective, population-based, randomised, open-label, non-inferiority trial. Lancet Oncol 22: 1240-1249, 2021.
85. Song J, Ma S, Sokoll LJ, Eguez RV, Höti N, Zhang H, Mohr P, Dua R, Patil D, May KD, *et al*: A panel of selected serum protein biomarkers for the detection of aggressive prostate cancer. Theranostics 11: 6214-6224, 2021.
86. Labiano S, Palazón A, Bolaños E, Azpilikueta A, Sánchez-Paulete AR, Morales-Kastresana A, Quetglas JI, Perez-Gracia JL, Gúrpide A, Rodriguez-Ruiz M, *et al*: Hypoxia-induced soluble CD137 in malignant cells blocks CD137L-costimulation as an immune escape mechanism. Oncoimmunology 5: e1062967, 2016.