Role of multi-omics in advancing the understanding and treatment of prostate cancer (Review)

LI YAN, PENGXIAO SU and XIAOKE SUN

Department of Urology, Honghui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi 710054, P.R. China

Received September 30, 2024; Accepted January 27, 2025

DOI: 10.3892/mmr.2025.13495

Abstract. The application of multi-omics methodologies, encompassing genomics, transcriptomics, proteomics, metabolomics and integrative genomics, has markedly enhanced the understanding of prostate cancer (PCa). These methods have facilitated the identification of molecular pathways and biomarkers crucial for the early detection, prognostic evaluation and personalized treatment of PCa. Studies using multi-omics technologies have elucidated how alterations in gene expression and protein interactions contribute to PCa progression and treatment resistance. Furthermore, the integration of multi-omics data has been used in the identification of novel therapeutic targets and the development of innovative treatment modalities, such as precision medicine. The evolving landscape of multi-omics research holds promise for not only deepening the understanding of PCa biology but also for fostering the development of more effective and tailored therapeutic interventions, ultimately improving patient outcomes. The present review aims to synthesize current findings from multi-omics studies associated with PCa and to assess their implications for the improvement of patient management and therapeutic outcomes. The insights provided may guide future research directions and clinical practices in the fight against PCa.

Contents

1. Introduction
2. Genomic research
3. Transcriptomic advances
4. Proteomic profiling
5. Metabolomics research
6. Application of single-cell sequencing
7. Synergy of multi-omics integration
8. Future perspectives in multi-omics research
9. Conclusion

Correspondence to: Professor Xiaoke Sun, Department of Urology, Honghui Hospital, Xi'an Jiaotong University, 555 Friendship East Road, South Gate, Beilin, Xi'an, Shaanxi 710054, P.R. China
E-mail: abcd_4570@qq.com

Key words: multi-omics, genomics, transcriptomics, proteomics, metabolomics, single-cell sequencing, prostate cancer

1. Introduction

Prostate cancer (PCa) is one of the most prevalent malignancies among men worldwide, and presents a significant public health concern (1). It is the second leading cause of cancer-associated mortality globally, with its incidence varying widely across different geographical groups and ethnic groups (1). Established risk factors include advancing age, family history and genetic predispositions, such as mutations in the BRCA1 and BRCA2 genes (2). In addition, lifestyle factors, including diet and obesity, are considered to contribute to the risk of developing PCa (3). Current therapeutic strategies for the management of PCa encompass a range of options, including active surveillance, radical prostatectomy, radiation therapy, androgen-deprivation therapy (ADT) and, for advanced stages, chemotherapy and immunotherapy (4). Despite these treatments, effective management remains challenging due to variability in disease progression and treatment responses among individuals (5).

Prostate-specific antigen (PSA) testing is widely used for the early diagnosis of PCa; however, it has several limitations. Elevated PSA levels are not specific to PCa and may also result from benign prostatic hyperplasia or prostatitis, leading to false-positive results and unnecessary biopsies (6). Furthermore, PSA does not differentiate between indolent and aggressive forms of PCa, which can complicate treatment decisions (7). The treatment of castration-resistant PCa (CRPC) also presents considerable challenges. CRPC is characterized by tumor progression despite the levels of testosterone being at levels typical of castration, often resulting in a poor prognosis and promoting a requirement for novel therapeutic modalities (8). Although advancements such as second-generation antiandrogens and targeted therapies have been achieved, the heterogeneity of CRPC leads to highly variable treatment responses among patients, indicating that more personalized approaches are necessary (9).

Advancements in multi-omics technologies, including genomics, transcriptomics, proteomics and metabolomics, have profoundly transformed cancer research by providing a comprehensive view of the molecular landscape of tumors (10).

Multi-omics approaches facilitate a deeper understanding of tumor heterogeneity and the molecular mechanisms underlying disease progression (11). Multi-omics methodologies are increasingly applied in PCa research, yielding promising results that enhance the understanding of PCa biology. For example, the integration of genomic and epigenomic data has facilitated the identification of novel therapeutic targets and biomarkers that may assist in earlier diagnosis and the development of more effective treatment strategies (12). In addition, alterations in certain pathways, such as androgen receptor (AR) signaling and metabolic reprogramming pathways, have been demonstrated to play crucial roles in the progression of PCa (13) (Fig. 1).

The present review aims to explore the advances in multi-omics technology applied to PCa research, emphasizing their potential to transform diagnostic, prognostic and therapeutic frameworks in the management of this disease. By synthesizing current knowledge on multi-omics applications in PCa, the review seeks to highlight how these innovations can offer new insights into patient stratification and therapeutic targets, ultimately leading to improved clinical outcomes. This exploration is not only timely but also crucial for advancing the understanding and management of PCa in an era increasingly driven by personalized medicine.

2. Genomic research

Genomic research over the past decade has fundamentally shifted the landscape of PCa diagnosis and treatment strategies. The characterization of mutations, such as those in BRCA1, BRCA2 and transmembrane protease, serine 2 (TMPRSS2)-ETS-related gene (ERG), has provided valuable insights into the mechanisms driving PCa and has ushered in the era of precision medicine. The implications for risk stratification and treatment decisions are profound, as clinicians now have access to tools that enable personalized therapy approaches. The ongoing integration of genomic mapping into clinical practice continues to hold promise for improving survival outcomes and the quality of life for men diagnosed with PCa.

Key findings from the last decade in PCa genomic studies. PCa has become a focus of intense genomic research over the last decade, which has provided insights into its pathogenesis and avenues for future therapeutic interventions. Key findings have highlighted the roles of several important genes, including BRCA1, BRCA2, partner and localizer of BRCA2 (PALB2), DNA mismatch repair gene (ATM), checkpoint kinase 2 (CHEK2), MutS homolog 2 (MSH2), MSH6, nibrin (NBN), TMPRSS2-ERG, TP53 and phosphatase and tensin homolog deleted on chromosome ten (PTEN) (Table I). The findings deepen understanding of the biological behavior of PCa and pave the way for the development of targeted therapies and personalized treatment strategies. Future research is essential to explore the therapeutic potential of targeting these genetic alterations, with the goal of improving outcomes for patients with PCa.

Robinson *et al* (14) conducted a comprehensive genomic analysis of advanced PCa, which identified that alterations in BRCA2 and ATM are particularly relevant to the aggressiveness and therapeutic response of the disease. While BRCA1 and BRCA2 mutations are well-established as risk factors for hereditary breast and ovarian cancer, they are increasingly being recognized as being associated with an increased risk and poorer outcomes in patients with PCa (15). PALB2 a gene involved in DNA damage repair, has also been identified as a significant risk factor for PCa. A study found that mutations in PALB2 are associated with an elevated risk of developing PCa and may impact survival rates, underscoring its importance in hereditary cancer predisposition (16). ATM is a key gene in the cellular response to DNA double-strand breaks, and its mutation predisposes individuals to PCa, as discussed in the PRACTICAL Consortium study (17). This mutation is considered a key germline variant that is important to consider in the genetic counseling of patients at risk. Similarly, CHEK2, which is involved in the DNA damage response, has been shown to harbor germline variants that contribute to cancer susceptibility, albeit with varying penetrance (18).

Deficiency in the DNA mismatch repair system, involving genes such as MSH2 and MSH6, has been implicated in PCa. Sharma *et al* (19) highlighted that the loss of the proteins encoded by these genes is associated with a distinct subset of aggressive tumors, highlighting the importance of genomic stability in PCa. Hereditary genes have been identified as contributors to PCA, but somatic alterations are also crucial in PCa pathology. Inherited mutations in NBN have been identified as a risk factor, with carriers of NBN mutations being significantly more likely to develop PCa, which highlights the importance of DNA double-strand break repair mechanisms in cancer susceptibility (20). Furthermore, mutations in TP53 and PTEN are well-documented in advanced PCa. As noted by Maxwell *et al* (21), TP53 alterations are significantly associated with poorer clinical outcomes, while PTEN loss, associated with increased tumor aggressiveness, drives the progression of PCa (22). The interplay between these genetic alterations and their collective impact on tumor biology and therapeutic resistance is an active area of ongoing research.

Implications of genomic research for risk stratification and treatment decisions. The integration of genomic data into clinical practice has greatly improved risk stratification in PCa. Genomic tests, such as the Decipher biopsy and Oncotype DX, utilize gene expression profiles to improve the classification of patients into risk groups, extending beyond traditional clinicopathological parameters (23). This stratification enables clinicians to identify patients at a higher risk of aggressive disease and to tailor treatment approaches accordingly. For instance, genomic profiling has been instrumental in guiding decisions regarding active surveillance compared with intervention. It has enabled patients with low genomic risk scores to avoid overtreatment, and those with high risk scores to be directed toward earlier and potentially more aggressive treatment options, including intensity-modulated radiotherapy or radical prostatectomy (24). However, the application of genomic profiling to guide treatment decisions, such as choosing between active surveillance and intervention, has certain limitations. Patients classified at low genomic risk may have aggressive disease characteristics not accounted for by existing models, potentially leading to undertreatment.

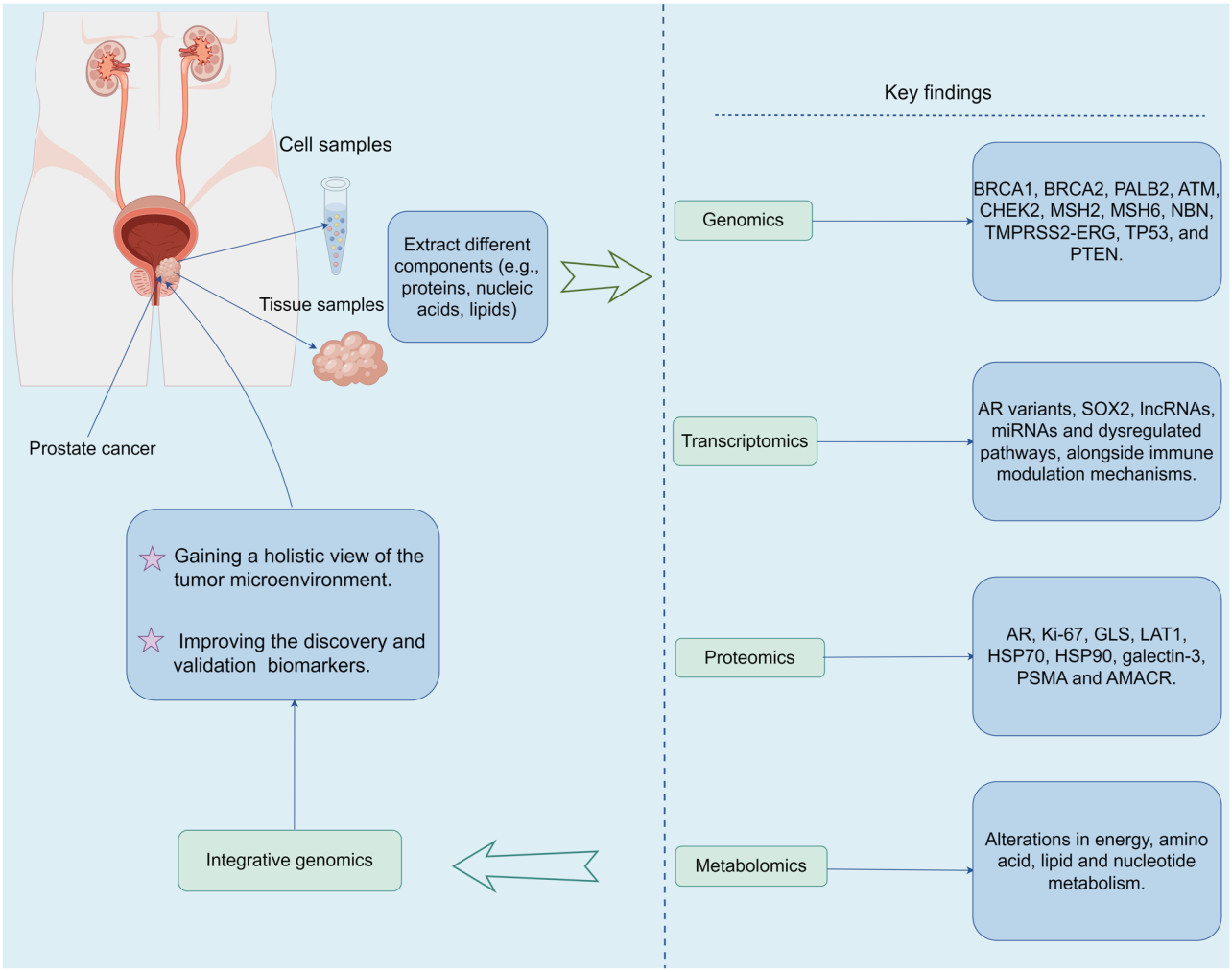

Figure 1. Summary of the application of multiple omics to PCa. Schematic illustrating numerous specific biomarkers, signaling pathway changes and metabolic changes associated with PCa that have been identified via multi-omics studies. The figure was generated by Figdraw (www.figdraw.com; copyright code, ATAPU55533). PCa, prostate cancer; PALB2, partner and localizer of BRCA2; ATM, DNA mismatch repair gene; CHEK2, checkpoint kinase 2; MSH2/6, MutS homolog 2/6; NBN, nibrin; TMPRSS2, transmembrane protease, serine 2; ERG, ETS-related gene; PTEN, phosphatase and tensin homolog deleted on chromosome ten; AR, androgen receptor; SOX2, sex determining region Y-box 2; lncRNAs, long non-coding RNAs; miRNAs, microRNAs; GLS, glutaminase; LAT1, L-type amino acid transporter 1; HSP70/90, heat shock protein 70/90; PSMA, prostate-specific membrane antigen; AMACR, a-methylacyl-CoA racemase.

Conversely, patients with high-risk scores may respond favorably to conservative management, indicating that genomic scores do not capture the full clinical complexity of PCa.

Genomic alterations also influence systemic therapies. For example, BRCA1/BRCA2 mutations have been found to be associated with sensitivity to therapies targeting DNA repair mechanisms, including poly (ADP ribose) polymerase (PARP) inhibitors (25). Similarly, alterations in AR signaling pathways, such as mutations and amplifications of the AR gene, can guide the use of AR-targeted therapies such as abiraterone and enzalutamide (26). However, the presence of AR signaling pathway alterations further complicates treatment decisions, as their presence does not guarantee the enhanced efficacy of AR-targeted therapies. Therefore, while genomic research is propelling the evolution of personalized treatment paradigms in PCa, clinicians must address the challenges associated with variability in research outcomes and the limitations of existing genomic tools to ensure optimal patient management.

Clinical applications of genomic mapping. A notable case study demonstrates the clinical application of genomic findings in a patient with metastatic CRPC (mCRPC) harboring a BRCA2 mutation. Following genomic profiling, the patient was treated with the PARP inhibitor olaparib, and imaging revealed a significant reduction in tumor burden. This case exemplifies how genomic data not only informs treatment eligibility but also directly impacts clinical outcomes (27). While this case highlights the potential for genomic data to inform therapy decisions and improve clinical outcomes, questions remain concerning the generalizability of such results, as individual patient responses can vary widely due to genetic and phenotypic differences.

Another example comes from a cohort of patients undergoing active surveillance, where genomic profiling revealed the presence of the TMPRSS2-ERG fusion gene. Patients who tested positive for this fusion exhibited higher rates of progression, prompting a reconsideration of their management strategy. In patients undergoing active surveillance,

Table I. Key findings from genomic studies on PCa in the last decade.

First author, year	Gene	Samples	Major findings	Location	(Refs.)
Robinson *et al*, 2015	BRCA2, BRCA1, ATM	Bone or soft tissue tumor biopsies from 150 patients with mCRPC	Frequency of BRCA2, BRCA1 and ATM aberrations in mCRPC is significantly higher compared with that in primary PCa	United States	(14)
Chi *et al*, 2023	BRCA2, BRCA1, ATM	Matched tumor tissue and circulating tumor DNA from patients with prostate cancer screened in PROfound	BRCA1, BRCA2 and ATM alterations were detected in both tumor tissue and circulating tumor DNA, highlighting the potential for liquid biopsies to inform treatment decisions	Various	(15)
Wokołorczyk *et al*, 2021	PALB2	5,472 unselected cases of PCa and 8,016 controls	PALB2 mutations predispose to an aggressive and lethal form of PCa	Poland	(16)
Karlsson *et al*, 2021	ATM	5,560 cases and 3,353 controls of European ancestry	Carriers of pathogenic ATM variants have an elevated risk of developing PCa and increased risk of earlier-onset disease presentation	Europe	(17)
Alorjani *et al*, 2023	CHEK2	74 patients with radical prostatectomy	CHEK2 mutation frequency 1.4% supports the role of genetic variants of this gene in the development of PCa	Jordan	(18)
Sharma *et al*, 2020	MSH2, MSH6	220 radical prostatectomy specimens	MSH2 and MSH6 protein loss is associated with significantly elevated PSA levels and helps predict tumor recurrence after radical prostatectomy	United States	(19)
Rusak *et al*, 2019	NBN	5,189 cases of PCa and 6,152 controls	NBN mutation predisposes to poor prognosis in PCa	Poland	(20)
Maxwell *et al*, 2022	TP53	31 PCa cases	Inherited pathogenic TP53 variants predispose to aggressive PCa	United States	(21)
Imada *et al*, 2021	PTEN	1,832 cases of PCa	PTEN somatic gene mutation is associated with increased overall mortality in patients with PCa	United States	(22)

PCa, prostate cancer; ATM, DNA mismatch repair gene; mCRPC, metastatic castration-resistant PCa; PALB2, partner and localizer of BRCA2; CHEK2, checkpoint kinase 2; MSH2/6, MutS homolog 2/6; NBN, nibrin; PTEN, phosphatase and tensin homolog deleted on chromosome ten.

the presence of TMPRSS2-ERG fusion and an increased genomic risk score were significantly associated with a higher likelihood of disease progression, demonstrating the potential for genomic data to alter clinical management plans (28). However, the reliability of the TMPRSS2-ERG fusion as a predictive biomarker remains inconsistent across studies. For instance, a meta-analysis found that the predictive significance of TMPRSS2-ERG fusion in prostate cancer is not universally supported, with a study showing no significant association between the fusion and disease progression (29). Additionally, a study by Álvarez-Garcia *et al* (30) highlighted the diversity of mechanisms leading to TMPRSS2-ERG fusion and questioned its clinical utility as a biomarker, emphasizing the need for further research to clarify its role. The risk of over-treatment based on genomic findings requires careful consideration.

Genomic mapping plays a critical role in the stratification of patients based on treatment response in PCa. For example, a study demonstrated that genomic alterations could guide therapy choices, thereby enhancing personalized treatment approaches (14). This stratification enabled clinicians to optimize therapeutic regimens and improve patient outcomes. However, the efficacy of such stratification relies on a thorough understanding of the underlying mechanisms and the potential impact of confounding factors on treatment responses. Therefore, while genomic mapping holds significant promise for improving PCa management, the ongoing evaluation of its clinical utility and the robustness of its predictive capabilities is essential to ensure that it translates into improved patient care.

3. Transcriptomic advances

Advancements in transcriptomic research for PCa have revolutionized the understanding of gene expression variability and enabled the identification of promising biomarkers. These have facilitated the generation of predictive models for treatment

Table II. Identification of new biomarkers for PCa.

First author, year	Biomarkers	Functions in PCa	(Refs.)
Yang *et al*, 2024	AR and its variants	AR-V7, a splice variant of AR mRNA with truncation of the ligand-binding domain, is a biomarker for resistance to AR axis-targeted therapies	(34)
de Wet *et al*, 2022	SOX2	SOX2 promotes PCa metastasis, lineage plasticity and treatment resistance by mediating the metabolic reprogramming of PCa cells	(35)
Fu *et al*, 2022	PCGEM1	lncRNA PCGEM1 promotes the progression of PCa by sponging miR-129-5p as a ceRNA of CDT1	(39)
Mu *et al*, 2022	MALAT1	lncRNA MALAT1 controls glucose metabolism and PCa progression by upregulating the MYBL2-mTOR axis	(40)
Zeng *et al*, 2021	miR-145	miR-145 suppresses the motility of PCa cells via the post-transcriptional downregulation of CDH2 expression; miR-145-CDH2 may be a potential target for intervention in PCa metastasis	(42)
Gui *et al*, 2017	miR-221/222	miR-221 and -222 function as oncogenes, promoting PCa cell proliferation and the development of CRPC	(43)
Pungsrinont *et al*, 2021	PI3K-AKT-mTOR	Alterations in the PI3K-AKT-mTOR pathway are associated with poor prognosis, driving tumor growth and metastasis	(45)
Guan *et al*, 2017	Wnt/β-catenin	Aberrant activation of Wnt/β-catenin signaling pathway is associated with the progression of PCa to an aggressive phenotype	(47)
Conley-LaComb *et al*, 2013	CXCL12/CXCR4	Activation of CXCL12 signaling through CXCR4 in PCa is driven by the loss of PTEN and subsequent activation of Akt; Akt-associated CXCL12/CXCR4 signaling promotes PCa growth	(51)

PCa, prostate cancer; AR, androgen receptor; SOX2, sex determining region Y-box 2; lncRNA, long non-coding RNA; PCGEM1, prostate cancer gene expression marker 1; miR, microRNA; ceRNA, competing endogenous RNA; CDT1, chromatin licensing and DNA replication factor 1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MYBL2, MYB proto-oncogene like 2; CDH2, cadherin-2; CRPC, castration-resistant prostate cancer; PI3K, phosphoinositide 3-kinase; CXCL12, chemokine C-X-C motif ligand 12; CXCR4, chemokine receptor 4; PTEN, phosphatase and tensin homolog deleted on chromosome ten.

response and paved the way for targeted therapies. As research evolves, the integration of transcriptomic data with other omics approaches is likely to yield further insights, further enhancing the precision of PCa management and improving patient outcomes.

Role of transcriptomics in understanding gene expression variability. Transcriptomics, the study of RNA transcripts produced by the genome under specific circumstances, has markedly improved the understanding of gene expression variability in PCa. By employing high-throughput sequencing and microarray technologies, the expression profiles of thousands of genes can be analyzed simultaneously, revealing the molecular complexities of PCa. This variability in gene expression is influenced by numerous factors, including genetic mutations, epigenetic changes and the tumor microenvironment (TME). Studies have demonstrated distinct transcriptional subtypes of PCa that are associated with clinical outcomes. For example, one landmark study comprehensively analyzed gene expression profiles associated with different grades of prostate tumors and discovered that specific gene sets associated with cell cycle regulation, androgen response and immune response significantly varied across these grades (31). In another study, the differential expression of the MYC oncogene and its downstream targets was implicated in PCa progression, which emphasizes the role of oncogenic signaling pathways in the etiology of the disease (32).

Transcriptomic analysis has led to the identification of alternative splicing events and non-coding RNAs that contribute to the complexity of gene regulation in PCa. For example, the long non-coding RNA (lncRNA) PCAT-1 has been shown to promote cell proliferation, and found to be upregulated in a subset of aggressive PCa cases, suggesting its potential as a therapeutic target (33). Thus, transcriptomics provides critical insights into the dynamic regulation of gene expression and its relevance to PCa pathogenesis.

Identification of novel biomarkers. Advances in transcriptomic research have provided valuable insights into the molecular landscape of PCa and revealed numerous novel therapeutic targets. Factors including AR variants (34), sex determining region Y-box 2 (SOX2) (35), lncRNAs, microRNAs (miRNAs), dysregulated pathways and immune modulation mechanisms, constitute promising areas for future drug development (Table II). Consideration of these findings together supports the clinical exploitation of these targets to provide more personalized and effective treatment strategies for patients with PCa. Furthermore, the continued integration of transcriptomic data with clinical outcomes will be essential for translating these discoveries into actionable therapies.

AR signaling is a cornerstone in the progression of PCa. Transcriptomic studies have identified AR splice variants, particularly AR splice variant 7 (AR-V7), which lack the ligand-binding domain and are associated with resistance to ADT. Notably, these studies indicate that targeting AR-V7 with small molecule inhibitors or RNA-targeting therapies may improve treatment outcomes in patients with CRPC (34,36). SOX2 has also been implicated in promoting PCa stem cell properties and tumor growth (37). High SOX2 expression is associated with a poor prognosis, suggesting the potential of SOX2 as a therapeutic target. Therefore, inhibitors targeting SOX2 signaling pathways may serve as novel strategies for the treatment of advanced PCa (38).

Advances in transcriptomics have underscored the role of lncRNAs in PCa pathogenesis. For example, lncRNA PCa gene expression marker 1 (PCGEM1) is upregulated in prostate tumors and is associated with cancer cell proliferation and migration (39). In addition, silencing PCGEM1 expression has been shown to reduce tumor growth *in vivo*, supporting its potential as a therapeutic target (39). Another lncRNA, metastasis associated lung adenocarcinoma transcript 1 (MALAT1), has been found to play an important role in the epithelial-mesenchymal transition (EMT) of PCa cells (40). By regulating the splicing of its target genes, MALAT1 attenuates EMT and potentially inhibits PCa metastasis (41). miRNAs are key regulatory molecules in gene expression that have been found to contribute to tumorigenesis in PCa. For example, miR-145 suppresses PCa cell proliferation by targeting multiple oncogenes (42). In addition, the loss of miR-145 expression is associated with advanced disease stages, suggesting the potential of miR-145 as a therapeutic agent that could be restored using miRNA mimic strategies. Furthermore, the miR-221/222 cluster is implicated in androgen resistance (43). Targeting this miRNA cluster has demonstrated promising results in re-sensitizing CRPC cells to androgen therapies (44), highlighting its potential as an adjunct treatment option.

Transcriptomic analyses have revealed dysregulation of the phosphoinositide 3-kinase-AKT-mTOR pathway in PCa, which is frequently associated with poor prognosis, tumor growth and metastasis (45). Therapeutic strategies targeting this pathway, such as AKT inhibitors, have shown some effectiveness and are being explored in clinical trials (46), suggesting that this pathway could be a viable target for novel PCa therapies. The Wnt/β-catenin signaling pathway is another critical area of interest identified through transcriptomic analysis. Aberrant activation of this pathway is associated with the progression of PCa to an aggressive phenotype (47). Targeting Wnt/β-catenin signaling with small molecule inhibitors has been suggested to represent a prospective therapeutic strategy, particularly in patients exhibiting dysregulation of this pathway (48).

A number of transcriptomic studies have focused on the interaction between PCa cells and the TME, particularly the immune landscape. These studies reveal that high expression levels of immune checkpoint molecules, along with T cell exhaustion markers, are associated with poor outcomes (49). Therefore, combining immune checkpoint inhibitors with therapies that modulate the TME offers the potential for new therapeutic approaches. In addition, the transcriptomic identification of cytokines and chemokines that facilitate tumor-immune cell interactions has uncovered promising targets for therapeutic intervention (50); specifically, therapeutic agents disrupting the chemokine C-X-C motif ligand 12/chemokine receptor 4 axis have been identified for further investigation, as they showed promise in the reversal of immune suppression in PCa (51).

Impact of transcriptomics on the development of targeted therapies for PCa. Insights gained from transcriptomic studies have been pivotal in the development of targeted therapies for PCa. As the molecular signatures of the disease are elucidated, it becomes possible to explore and refine therapeutic strategies targeting specific dysregulated pathways. A notable example is the AR, a critical driver of PCa. Transcriptomic analyses have identified mutations and splice variants of the AR gene that confer resistance to standard ADTs (14). These findings have facilitated the development of novel therapeutic agents that target the wild-type receptor and its variants. Drugs such as enzalutamide and abiraterone are now utilized for the treatment of advanced PCa and have significantly improved patient outcomes (52).

Transcriptomic profiling has identified pathways involved in cell survival, apoptosis and proliferation that are dysregulated in PCa, leading to the discovery of novel intervention targets. For example, inhibitors targeting the cell cycle regulatory protein CDK4/6 have shown promise in clinical trials, particularly in tumors expressing high levels of the relevant transcripts (53,54). However, the heterogeneity of transcriptomic profiles across different tumor stages and patient demographics may affect the reliability of these targets. In addition, transcriptomic analyses of the TME have opened new avenues for immunotherapy in PCa (55). By identifying expression profiles associated with immune evasion, combinatorial therapeutic strategies are being explored that integrate immune checkpoint inhibitors with conventional treatments to harness the immune system in PCa (56).

In summary, transcriptomics not only provides information about the molecular mechanisms associated with PCa but also impacts therapeutic approaches. By identifying novel biomarkers, predicting treatment responses and uncovering novel therapeutic targets, transcriptomic research lays the groundwork for the continued advancement of targeted and personalized therapies in PCa management.

4. Proteomic profiling

The integration of proteomics into PCa research has yielded further insights into the molecular underpinnings of the disease. Advances in analytical technologies such as mass spectrometry (MS), and the identification of novel protein biomarkers have improved the prospects for PCa diagnosis and treatment. By leveraging proteomic data, clinicians can gain a deeper understanding of tumor biology, paving the way for more effective and personalized interventions tailored to individual patients. Continued exploration of the proteomic landscape will improve the current knowledge of the molecular mechanisms associated with PCa and may also revolutionize therapeutic strategies.

Techniques used in proteomics. Proteomics is an expansive field that focuses on the large-scale study of proteins,

Table III. Protein biomarkers identified in PCa.

First author, year	Proteins	Mechanism of action	Clinical application	(Refs.)
Aurilio *et al*, 2020	AR	AR plays a key role in the progression of PCa and its resistance to endocrine therapy	Targeting AR signaling is a cornerstone of PCa treatment	(61)
Song *et al*, 2024	Ki-67	Ki-67 expression level is a proliferation marker in PCa	Ki-67 is used clinically as a prognostic marker for determining the aggressiveness of prostate tumors	(63)
Xu *et al*, 2021	GLS	GLS is a catalyst in glutamine metabolism, which is essential for cellular bioenergetics and anabolic processes in rapidly proliferating cancer cells	Inhibitors of GLS, such as CB-839, are being investigated in clinical trials for their potential in treating advanced PCa	(64)
Xu *et al*, 2016	LAT1	LAT1 is pivotal for the uptake of amino acids and other metabolites essential for tumor growth and metabolism	LAT1 inhibitors have shown the potential to disrupt amino acid supply and diminish tumor growth	(68)
Hoter *et al*, 2019	HSP70 and HSP90	Elevated levels of HSPs, such as HSP70 and HSP90 in PCa, are associated with increased tumor survival and resistance to chemotherapy	HSP90 inhibitors disrupt client protein stability and promote apoptosis in cancer cells	(70)
Souza *et al*, 2023	Galectin-3	Galectin-3 promotes tumor growth and metastasis through its effects on the tumor microenvironment	Galectin-3 inhibitors may reduce tumor growth and improve treatment outcomes	(74)
Wang *et al*, 2022	PSMA	PSMA regulates AR activity and may contribute to tumor growth and progression via its enzymatic activity	PSMA-targeted radioligand therapy has demonstrated significant clinical efficacy, providing a new option for patients with mCRPC	(76)
Fu *et al*, 2021	AMACR	AMACR facilitates the conversion of α-methylacyl-CoA to its racemic forms, contributing to altered lipid metabolism in tumor cells	Elevated levels of AMACR in prostate biopsy specimens are associated with cancer presence and aggressiveness, helping to distinguish between benign and malignant lesions	(79)

PCa, prostate cancer; AR, androgen receptor; GLS, glutaminase; LAT1, L-type amino acid transporter 1; HSP, heat shock proteins; PSMA, prostate-specific membrane antigen; mCRPC, metastatic castration-resistant prostate cancer; AMACR, α-methylacyl-CoA racemase.

particularly in terms of their functions and structures. In the context of PCa, one of the most critical proteomics techniques is MS. This technique sensitively detects proteins and is key in the identification and quantification of protein expression across different phases of PCa progression.

The most frequently used form of MS is liquid chromatography-tandem MS, which facilitates the separation and identification of complex protein mixtures. Notably, it is able to analyze protein post-translational modifications, which are crucial in cancer biology (57). Advancements in MS technology, including improved resolution, sensitivity and speed, have greatly enhanced its ability to identify low-abundance proteins that may serve as potential biomarkers for the early diagnosis and monitoring of PCa (58).

Techniques such as two-dimensional gel electrophoresis (2-DE) and affinity-based methods can be employed alongside MS. 2-DE separates proteins based on their isoelectric point and molecular weight, while affinity-based methods target specific proteins or post-translational modifications (59). Furthermore, high-throughput proteomic platforms enable the large-scale screening of tissue samples, yielding valuable insights into the protein landscapes associated with PCa pathology (60).

Protein biomarkers identified in PCa. The exploration of proteomic alterations in PCa has unveiled a plethora of potential biomarkers and therapeutic targets. Elucidation of the specific roles of these proteins in tumor biology offers opportunities for the development of novel clinical applications, such as improved diagnostics or targeted therapies (Table III). As research advances, the integration of proteomic data into clinical practice holds promise for personalized treatment strategies in PCa management. Continuous collaboration between basic research and clinical application is essential to translate these findings into therapeutic interventions that improve patient outcomes.

The AR plays a pivotal role in PCa progression. Alterations in protein expression, mutations and splice variants such

as AR-V7 are implicated in the development of CRPC. These changes confer resistance to ADTs by promoting AR signaling, even in low-androgen environments (61). Targeting AR signaling remains a cornerstone of PCa treatment, with second-generation anti-androgens, including enzalutamide and abiraterone, showing efficacy against CRPC. Furthermore, circulating AR-V7 has been identified in patients with PCa, and thus has emerged as a crucial biomarker for predicting resistance to AR-targeted therapies, thereby helping to guide treatment decisions towards alternative therapies such as taxanes (62).

Ki-67 is a nuclear protein associated with cellular proliferation that serves as a proliferation marker in various types of cancer, including PCa. High Ki-67 expression is associated with a poor prognosis and aggressive tumor behavior, indicating that tumors with elevated Ki-67 are more likely to grow and evade treatment (63). Ki-67 is used clinically as a prognostic marker to determine the aggressiveness of prostate tumors. Testing for Ki-67 levels, in conjunction with other clinical parameters, can help to guide treatment strategies, particularly in patients with intermediate-risk disease who may benefit from more aggressive therapies (63).

Glutaminase (GLS) plays a critical role in glutamine metabolism, which is essential for cellular bioenergetics and anabolic processes in rapidly proliferating cancer cells. Elevated GLS activity is associated with increased cancer cell proliferation and survival, particularly under the nutrient deprivation conditions common in solid tumors (64). Inhibitors of GLS, such as CB-839, are being investigated in clinical trials for their potential in treating advanced PCa, particularly in combination with conventional therapies (65). Targeting metabolic pathways offers a novel strategy, potentially overcoming resistance mechanisms associated with traditional hormonal therapies.

Nutrient transporters, such as L-type amino acid transporter 1 (LAT1), have been demonstrated to serve an important role in PCa cells (66). Other notable nutrient transporters include the solute carrier family 1 member 5, which is involved in glutamine uptake and has been shown to be upregulated in various cancers, including PCa (67). Additionally, the solute carrier family 7 member 5 transporter, which facilitates the uptake of large neutral amino acids, has also been identified as a key player in cancer cell metabolism and proliferation. The activity of these transporters is often influenced by the composition of the microenvironment and can be targeted for therapeutic intervention (67). These transporters are pivotal for the uptake of amino acids and other metabolites essential for tumor growth and metabolism, and the dysregulated expression of these transporters contributes to the aggressive behavior of PCa cells (68). The inhibition of nutrient transporters appears to be a promising therapeutic strategy; LAT1 inhibitors such as JPH203 have shown the potential to disrupt amino acid supply and diminish tumor growth (69). These strategies are being explored in basic research and may provide a complementary treatment method to existing therapies in the future.

Heat shock proteins (HSPs) are critical in protein folding, which protects cells from stress-induced apoptosis (70). In PCa, elevated levels of HSPs, including HSP70 and HSP90, are associated with increased tumor survival and resistance to chemotherapy (70). Their ability to stabilize oncogenic proteins further increases cancer cell viability. Targeting HSPs is being investigated as a therapeutic strategy for PCa. HSP90 inhibitors, such as tanespimycin, have been shown to disrupt the stability of client proteins, such as mutant p53 and AR, and to promote apoptosis in cancer cells (71). Clinical trials evaluating HSP inhibitors, such as tanespimycin, are underway and aim to assess their efficacy in conjunction with standard PCa treatments (72). Other HSPs, such as HSP20, HSP40, HSP60 and HSP80, are also being investigated for their roles in cancer and potential therapeutic applications (73).

Galectin-3 is a member of the galectin family of lectins, which is involved in various biological processes, including cell proliferation, apoptosis and inflammation (74). Galectin-3 has been shown to promote tumor growth and metastasis through its effects on the TME (74). In addition, elevated serum levels of galectin-3 have been linked to a poor prognosis in patients with PCa (75). Exploration of the potential of galectin-3 as a therapeutic target indicates that galectin-3 inhibitors have the ability to reduce tumor growth and improve treatment outcomes (75).

Prostate-specific membrane antigen (PSMA) is a transmembrane protein that is expressed in higher levels in PCa cells than in normal prostate tissue. It plays a role in the regulation of AR activity and may also contribute to tumor growth and progression via its enzymatic activity (76). PSMA-targeted therapies, such as PSMA-617, a radiolabeled small molecule, have shown promise in the imaging and treatment of advanced PCa. PSMA-targeted radioligand therapy has demonstrated significant clinical efficacy, and PSMA-617 has been approved by the FDA as a new radiotherapeutic option for patients with mCRPC (77). Furthermore, PSMA can also be used as a clinical biomarker for patient stratification (78).

α-Methylacyl-CoA racemase (AMACR) is an enzyme implicated in fatty acid metabolism that has been found to be upregulated in PCa cells. It facilitates the conversion of α-methylacyl-CoA to its racemic forms, contributing to altered lipid metabolism in tumor cells (79). AMACR has been explored as a diagnostic marker in PCa, particularly for use in histopathological assessments. This has revealed that elevated levels of AMACR in prostate biopsy specimens are associated with the presence and aggressiveness of cancer, making it a useful biomarker to assist pathologists in distinguishing between benign and malignant lesions (80).

Progress in proteomics in PCa TME research. The complexity of the TME presents considerable challenges in PCa research. Proteomics has been vital in characterizing the TME, which consists of cancer cells, stromal cells and extracellular matrix components, all of which interact dynamically to promote tumor growth and metastasis (81). A proteomic study has highlighted the shifts in the protein composition of the TME in response to oncogenic signaling and therapeutic interventions (82). Tumor-associated macrophages and their secretory profiles have been found to be associated with changes in the extracellular matrix composition, thereby influencing tumor progression (82). These intricate interactions underscore the potential of proteomic methodologies to elucidate the cross-talk between PCa cells and the surrounding stromal components.Spatial proteomics has been used to investigate the heterogeneity of protein expression within the TME.

Techniques such as imaging mass cytometry have enabled the protein distributions in tissue sections to be mapped, thereby revealing the spatial organization of proteins involved in immune evasion and treatment resistance (83). Such insights are crucial for the development of novel therapeutic targets aimed at remodeling the TME to inhibit tumor growth and improve patient outcomes. While proteomics has been instrumental in elucidating interactions within the TME in PCa, careful consideration of the methodologies employed and the variability of findings is essential. Understanding these nuances will be key in the development of novel therapeutic targets aimed at modulating the TME to inhibit tumor growth and, ultimately, improve patient outcomes.

5. Metabolomics research

The application of metabolomics in PCa research is enhancing the general understanding of tumor biology. By leveraging cutting-edge technologies and integrating metabolomic data with clinical outcomes, it is possible to identify key metabolic alterations and potential biomarkers to inform early detection and treatment strategies. As the complex metabolomic landscape of PCa becomes more defined, the promise of personalized medicine becomes increasingly tangible, ultimately benefiting patients through improved diagnosis and tailored therapeutic approaches.

Overview of metabolomics methods and technologies. Metabolomics is a powerful analytical approach designed to characterize all the metabolites present in biological samples, offering insights into metabolic changes associated with various diseases, including cancer. In PCa research, several methodologies are being employed to analyze metabolomic profiles and elucidate the underlying biochemical pathways that contribute to tumorigenesis and progression. The primary techniques utilized in metabolomics include MS and nuclear magnetic resonance (NMR) spectroscopy. MS, particularly when combined with chromatography methods such as gas or liquid chromatography, allows for the sensitive detection, identification and quantification of metabolites in complex biological matrices. The high sensitivity and resolution of modern mass spectrometers allow low-abundance metabolites to be detected, which can be crucial in cancer (84).

NMR spectroscopy is a non-destructive technique for analyzing metabolites in a sample and providing structural information. Although it is less sensitive than MS, NMR is valuable for quantifying metabolites in intact tissues, preserving the biological context of the sample (85). Furthermore, advanced bioinformatics tools are essential in metabolomics research. These tools are used for data processing, statistical analysis and the interpretation of complex metabolomic datasets. Computational techniques such as multivariate analysis, machine learning (ML) and pathway enrichment analysis contribute to the identification of key metabolic pathways disrupted in PCa (86).

Key metabolic alterations in PCa. Metabolomics has emerged as a powerful tool in cancer research, offering insights into the biochemical mechanisms of tumor biology. Key findings highlight alterations in energy, amino acid, lipid and nucleotide metabolism, all of which contribute to the aggressive nature of this malignancy (Table IV). In future research, a focus on the integration of metabolomic data with genomic and proteomic information is necessary to fully understand the complexities of PCa biology and to refine therapeutic strategies.

One of the hallmarks of cancer is the switch from oxidative phosphorylation to aerobic glycolysis, known as the Warburg effect (87). In PCa tissues, altered levels of key metabolites associated with energy metabolism have been detected, including increased lactate and decreased citric acid cycle intermediates (88). In addition to supporting rapid proliferation, this shift influences the TME by promoting acidotic conditions, facilitating invasion and metastasis (89).

PCa cells exhibit distinct patterns of amino acid metabolism. Notably, increased levels of branched-chain amino acids (BCAAs), including leucine and valine, have been identified in patients with PCa compared with healthy controls (90). In addition, tryptophan metabolism, particularly its kynurenine pathway, has been implicated in immune evasion mechanisms employed by tumors (90). These alterations indicate potential biomarkers and therapeutic targets, as the availability of amino acids can influence tumor growth.

Lipid metabolism is notably altered in PCa, with increased levels of specific fatty acids, sterols and phospholipids. A previous review of metabolomic studies highlighted that levels of unsaturated fatty acids, notably arachidonic acid, are elevated in PCa, which suggests increased membrane fluidity and a potential role in cancer progression (91). Furthermore, sterol metabolism, particularly the accumulation of cholesterol and its metabolites, contributes to membrane biogenesis and the activation of signaling pathways that promote oncogenesis (92).

PCa cells exhibit heightened nucleotide synthesis, as evidenced by elevated levels of purines and pyrimidines, which supports the rapid proliferation of cancer cells (93). Targeting nucleotide metabolism pathways is a novel therapeutic strategy that may hinder cancer cell growth by disrupting the synthesis of nucleotides.

Metabolomic analyses have revealed alterations in carbohydrate metabolism pathways, including increased glucose uptake and metabolism. Elevated hexosamine biosynthesis in PCa has been shown to contribute to glycosylation changes in proteins associated with oncogenic signaling (94). Furthermore, changes in glycogen metabolism have been documented, further emphasizing the shifts in energy substrates utilized by cancer cells (94).

The identification of these metabolic alterations has implications for the management of PCa. In particular, metabolomic profiling may aid in risk stratification and the development of personalized medicine approaches. For instance, elevated BCAAs and lipid alterations may serve as potential biomarkers for the early detection and monitoring of disease progression (95). In addition, targeting these metabolic pathways provides opportunities for innovative treatment options, such as metabolic inhibitors that disrupt cancer cell energetics and proliferation.

Integrating metabolomic features with clinical data to improve diagnosis. The integration of metabolomic data with clinical parameters has the potential to enhance diagnosis and

Table IV. Key metabolic alterations in PCa.

First author, year	Metabolic classification	Metabolic alterations associated with PCa	(Refs.)
Chetta *et al*, 2023	Altered energy metabolism	Levels of key metabolites associated with energy metabolism are altered, including increased lactic acid and decreased citric acid cycle intermediates; this transformation supports the rapid proliferation of PCa cells, and promotes their invasion and metastasis under acidic conditions	(88)
Chen *et al*, 2024	Amino acid metabolism	Levels of branched-chain amino acids such as leucine and valine are significantly increased in PCa compared with normal tissue; tryptophan metabolism, particularly its kynurenine pathway, is implicated in immune evasion mechanisms employed by tumors	(90)
Zeković *et al*, 2023	Lipid metabolism dysregulation	Levels of unsaturated fatty acids, particularly arachidonic acid, are elevated in PCa, suggesting a role in cancer progression	(91)
Škara *et al*, 2021	Lipid metabolism dysregulation	Cholesterol metabolism, including increased levels of cholesterol and its metabolites, promote tumorigenesis	(92)
Yun *et al*, 2015	Nucleotide metabolism	PCa cells show heightened nucleotide synthesis, as evidenced by elevated levels of purines and pyrimidines	(93)
Srihari *et al*, 2018	Carbohydrate metabolism	Hexosamine biosynthesis is elevated in PCa, and contributes to glycosylation changes in proteins associated with oncogenic signaling	(94)

PCa, prostate cancer.

prognostication in PCa. By identifying associations between metabolomic findings and clinical outcomes, it may be possible to develop a more comprehensive understanding of the disease and identify patterns that could inform personalized treatment strategies. For example, studies have demonstrated that panels of metabolites combined with clinical data, such as PSA levels, Gleason scores and imaging findings, can be used to improve diagnostic accuracy (96,97). In addition, a multi-analyte metabolomic assay incorporating metabolomic signatures with conventional markers was shown to provide improved results in the prediction of malignancy in patients with elevated PSA levels (98). Nevertheless, variability in study design, sample sizes and metabolic profiling techniques may affect the reliability and generalizability of these findings.

The application of ML approaches to metabolomic datasets is useful in the identification of novel metabolites as potential prognostic markers. The classification of patients with PCa based on their metabolomic profiles can contribute to the prediction of disease progression, response to therapy and overall survival (99). ML models can also help to refine treatment decisions, allowing clinicians to tailor interventions based on the metabolic signature of each individual patient (100). However, while ML models have the capacity to refine treatment decisions tailored to specific metabolic signatures, concerns about overfitting and the requirement for external validation should not be overlooked (100).

As metabolomics continues to evolve, its integration with other omics technologies, such as genomics, proteomics and transcriptomics, may provide a holistic view of the tumor landscape. This multi-omics approach is expected to yield deeper insights into the molecular mechanisms associated with PCa, but the complexities associated with data integration and interpretation present ongoing challenges. Ultimately, addressing these issues will be crucial in facilitating the development of more effective diagnostic and therapeutic strategies.

6. Application of single-cell sequencing

The integration of single-cell sequencing technology into PCa research has been transformative in offering valuable insights into this heterogeneous disease. By dissecting the cellular composition and functional characteristics of tumors at unprecedented resolution, it is possible to identify critical driver cell types and pathways associated with disease progression and therapeutic resistance (101). The knowledge obtained by single-cell sequencing has profound implications for the development of personalized treatment strategies, and creates a foundation for more effective and tailored therapeutic interventions for patients with PCa.

Advances in single-cell technology in PCa. Single-cell sequencing technology has emerged as a groundbreaking tool for understanding the intratumoral heterogeneity and cellular complexity of PCa (102). This technology enables individual cells to be analyzed, thereby providing insights that are not possible in bulk tissue analyses. Advancements in single-cell RNA sequencing, single-cell DNA sequencing and single-cell assay for transposase-accessible chromatin sequencing have markedly improved the general understanding of PCa biology (102).

Single-cell RNA sequencing allows the transcriptomes of thousands of individual cells to be profiled, leading to the identification of distinct cellular populations within tumor (103). For example, a recent study has revealed the presence of previously unrecognized subpopulations of tumor cells that exhibit unique gene expression profiles associated with differential responses to therapy (104). Furthermore, spatial transcriptomics, which combines single-cell RNA sequencing with spatial information, is a novel technique that can characterize the spatial organization of tumor cells within the TME (105), which is critical for understanding cellular interactions and signaling pathways in PCa.

Advancements in droplet-based and microfluidic technologies have enabled the high-throughput analysis of single cells, which has major implications for large-scale studies of PCa (106). Techniques such as 10x Genomics Chromium and Seq-Well have made it feasible to examine thousands of individual cells simultaneously, which greatly increases throughput and reduces costs (105). These methods facilitate the identification of rare cell populations, which may have critical implications for tumor progression and treatment response.

Understanding tumor heterogeneity and microenvironment. A critical finding from single-cell sequencing in PCa is the extensive intratumoral heterogeneity that exists among cancer cells. Different clones within a single tumor can exhibit divergent genetic and phenotypic characteristics, contributing to variable responses to therapy and disease progression (104). For instance, single-cell RNA sequencing has identified distinct basal and luminal PCa subtypes, with variations in metabolic and signaling pathways that can influence outcomes following therapies such as ADT (105).

Single-cell technologies have been instrumental in elucidating the role of the TME in PCa. The TME comprises not only tumor cells but also stromal cells, immune cells and extracellular matrix components, all of which profoundly influence cancer progression (107). Single cell RNA sequencing has facilitated the characterization of immune cell populations infiltrating prostate tumors, providing insights into how these cells may facilitate or inhibit tumor growth. For example, a recent study identified a subset of immunosuppressive macrophages that contribute to tumor immune evasion (108).

The identification of specific cell types that contribute to cancer progression and treatment resistance is crucial. Cancer stem cells (CSCs) have the ability to drive tumor growth and metastasis (109). Single-cell technologies have identified markers associated with CSCs, highlighting their potential as targets for therapy (110). The insights obtained from single-cell studies have profound implications for understanding cancer cell plasticity. For example, the identification of hybrid states, where tumor cells adopt features of different lineages, helps to explain the emergence of treatment resistance and metastasis (111).

Single-cell sequencing has revolutionized PCa research by enabling the exploration of cellular heterogeneity within tumors (112). This approach facilitates the identification of distinct cell populations, including tumor-initiating cells and immune subsets, thereby deepening understanding of the TME and cancer progression (112). However, discrepancies in findings across studies raise concerns about reproducibility. For example, differences in sequencing techniques and data analysis pipelines can lead to inconsistent interpretations of cellular states and their functional roles (113). Furthermore, the resolution of single-cell data may overlook the influence of cell-cell interactions, limiting the scope of insights into tumor biology (114). Thus, while single-cell sequencing provides invaluable data for the advancement of PCa research, careful consideration of methodological variations is crucial for drawing robust and reliable conclusions.

7. Synergy of multi-omics integration

While the integration of multi-omics approaches presents unparalleled opportunities to advance the understanding of PCa and improve biomarker discovery, it is critical to recognize and overcome the associated challenges. Collaborations among researchers, clinicians and bioinformaticians, along with the implementation of standardized practices, are essential to unlock the potential of multi-omics strategies in elucidating the complexities of PCa and other malignancies.

Integrating data from various omics techniques. The advent of multi-omics approaches, encompassing genomics, transcriptomics, proteomics, metabolomics and epigenomics, has provided substantial insights into cancer biology, including PCa. By integrating diverse datasets from different omics technologies, a holistic view of the TME can be gained, which facilitates a deeper understanding of the molecular mechanisms driving disease progression, metastasis and therapeutic resistance.

One of the critical advantages of multi-omics integration is its ability to elucidate the complex interplay between genetic alterations, gene expression profiles, post-transcriptional modifications, protein interactions and metabolic changes within tumor cells. For example, the integration of genomic and transcriptomic data can be used to identify key driver mutations and their downstream effects on gene expression, providing a more accurate delineation of cancer subtypes (115). This integrative approach also allows specific pathways that might be targeted for therapeutic intervention to be identified. Furthermore, the combination of different omics data facilitates the discovery and validation of biomarkers (Fig. 2). Biomarkers derived through multi-omics approaches have the potential to be more specific and sensitive, thereby improving the screening, diagnosis and prognosis of PCa. For example, the integration of metabolomic profiles with genomic data has revealed distinctive metabolic signatures associated with tumor aggressiveness, which improves the predictive capability of biomarkers beyond that of individual omics datasets (116).

Multi-omics integration facilitates the identification of biomarkers that reflect the complexity of interactions between tumor heterogeneity and the TME (Fig. 2). By analyzing data from various sources, it is possible to identify tumor cell-intrinsic markers and markers associated with the TME, including immune cell infiltration and stromal interactions. This comprehensive perspective is critical for the development of targeted therapies and personalized treatment strategies, offering insights that may help to address variations in patient responses to therapies (117).

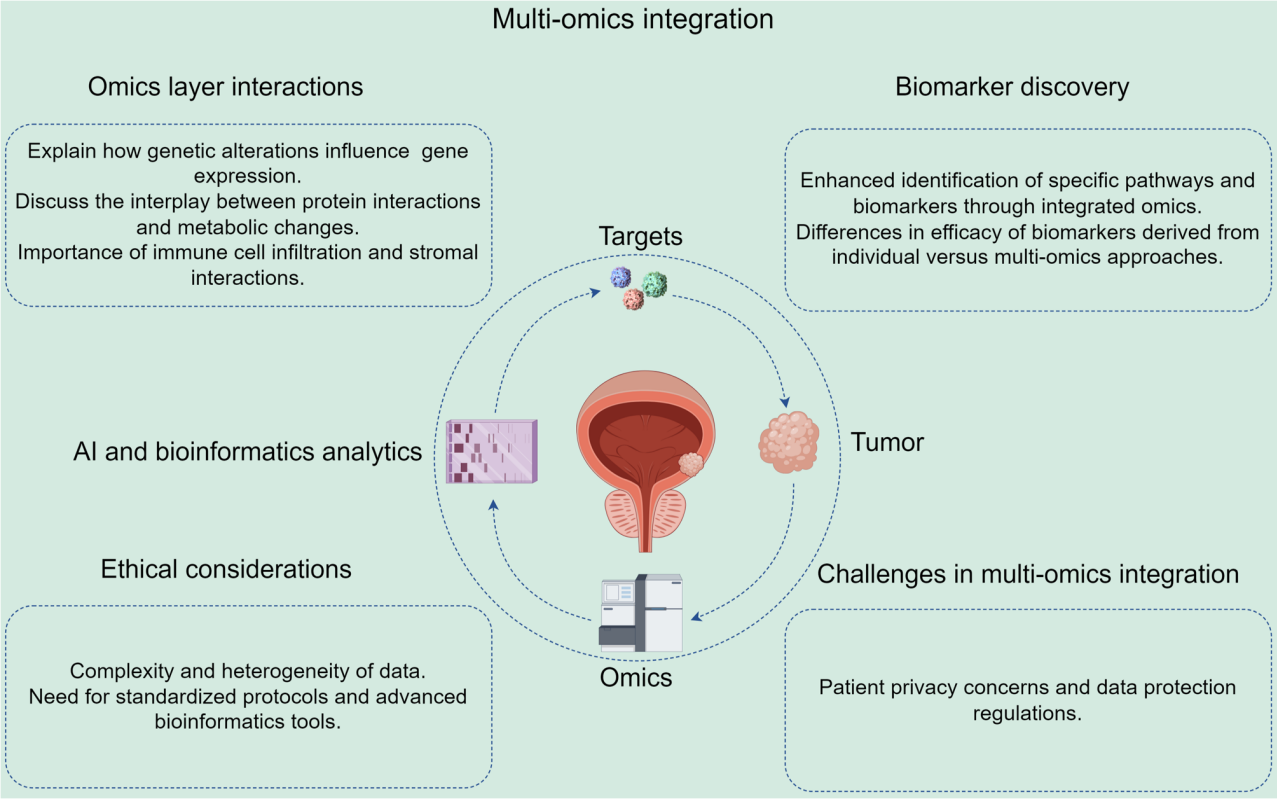

Figure 2. Demonstration of the application of multi-omics integration in prostate cancer. The figure was generated by Figdraw (www.figdraw.com; copyright code, UUAIAdd8b8).

Challenges of multi-omics data integration. While the potential for multi-omics integration is immense, there are notable challenges to overcome, particularly in data standardization, integration methodologies and bioinformatics analysis tools (11). The inherent heterogeneity of omics data presents a major barrier; for example, discrepancies in measurement techniques and data formats can complicate integration efforts (118). The establishment of effective standardization protocols is necessary to ensure comparability across studies (119). Various integration methods, including statistical learning techniques such as multi-factor analysis and ML algorithms, and computational frameworks such as Multi-Omics Factor Analysis, are crucial for managing these data types effectively (119). However, the application of advanced bioinformatics tools, including network-based approaches, is able to elucidate biologically meaningful interactions despite data complexity (86).

A primary obstacle to multi-omics integration is the inherent complexity and heterogeneity of the generated data (Fig. 2). Each omics technique produces vast amounts of information, often with varying scales, measures and corresponding analysis methods. This creates substantial analytical and interpretative challenges, necessitating sophisticated strategies to integrate and interpret the diverse datasets (117). In addition, the integration of multi-omics data requires robust bioinformatics tools and expertise. Advanced statistical methods and ML algorithms are essential for effective data processing, normalization and integration. However, the development and implementation of these tools has not kept up with the pace of data generation. Consequently, it is urgently necessary for ongoing research to focus on the improvement of computational methodologies for handling multi-omics data, to enable the extraction of meaningful biological insights (120).

Another challenge is the lack of standardized protocols for multi-omics studies, leading to inconsistencies in data collection, processing and analysis across different studies. Standardization is required not only for methodological procedures but also for data representation, which is essential for accurate comparisons and meta-analyses in PCa research (121). Collaborative initiatives and consortia focused on the establishment of standardized practices may help to address these issues and promote the wider adoption of multi-omics approaches in clinical settings. For example, the Multi-Omics for Health and Disease consortium of the NIH National Human Genome Research Institute is working to validate and enhance generalizable multi-omics approaches to identify meaningful biological changes related to health and disease in ancestrally diverse populations (122). Additionally, the National Microbiology Data Collaborative EDGE initiative aims to develop data harmonization, integration, visualization and analysis methods for multi-omics datasets (122).

The integration of multi-omics data in clinical settings poses ethical considerations and privacy concerns for patients (123) (Fig. 2). A major challenge is ensuring the anonymity and confidentiality of patient information, as genomic data can be uniquely identifying (123). The implementation of stringent data protection measures and adherence to regulatory guidelines is essential for safeguarding sensitive information (124). Furthermore, discrepancies in data integration methodologies can lead to inconsistent results, complicating

interpretations and clinical applications (125). For example, variations in study cohorts and analytical frameworks may yield conflicting biological insights, hindering reproducibility and eroding trust in multi-omics approaches (126). Addressing these challenges is essential for the ethical advancement of PCa research.

8. Future perspectives in multi-omics research

Multi-omics research has emerged as a cornerstone for advancing the understanding and treatment of PCa, as it has been key to the discovery of some of the complex molecular underpinnings of PCa, thereby leading to improvements in clinical outcomes. This section of the review aims to outline the future perspectives on multi-omics research, focusing on its clinical applications, the roles of artificial intelligence (AI) and ML, and the importance of collaborative efforts in this field.

The landscape of PCa treatment is evolving due to the use of multi-omics data, which has revealed novel therapeutic avenues. One key advancement is the use of PARP inhibitors, which has shown efficacy in patients with PCa harboring BRCA1/BRCA2 mutations (127). The TRIUMPH trial, which investigated rucaparib monotherapy in patients with metastatic hormone-sensitive prostate cancer harboring germline homologous recombination repair gene mutations, showed some clinical responses without concurrent ADT. However, the pre-specified efficacy threshold was not met. At present, there is a lack of other clinical trials reporting more encouraging results for PARP inhibitors in PCa (128). Furthermore, the integration of multi-omics approaches has deepened the understanding of targeted therapies, such as AKT inhibitors, which have shown promising outcomes in preclinical models and early-phase clinical trials, warranting further exploration in larger cohorts (129). In addition, the role of immunotherapy has garnered attention, particularly the use of immune checkpoint inhibitors, which may provide synergistic antitumor effects when used in combination with traditional therapies (130). Collectively, these advancements promote a shift in PCa management, emphasizing personalized treatment strategies informed by comprehensive omics analyses, which is ultimately paving the way for improved patient outcomes and refined clinical practices. The clinical applicability of multi-omics in PCa is substantial and continues to evolve as more data and insights are gathered. A particularly promising aspect is the development of personalized treatment plans that harness the distinct molecular profiles of tumors (131).

Multi-omics approaches can improve strategies for the screening and early detection of PCa. A combination of genomic, proteomic and metabolomic markers can be utilized to improve the sensitivity and specificity of current screening methods. A study by Sinha *et al* (132) demonstrated the ability of multi-omics to uncover biomarker signatures predicting aggressiveness in prostate tumors, potentially enabling earlier interventions and improved prognostic outcomes. However, it is essential to validate these signatures in larger, diverse cohorts and to explore their integration into clinical settings as part of routine screenings.

AI and ML technologies are vital tools for analyzing complex multi-omics data. Given the vast and intricate datasets generated through genomic, transcriptomic and proteomic analyses, conventional analytical methods often fail to extract meaningful patterns. By leveraging AI and ML algorithms, it is possible to analyze large-scale data more efficiently and effectively (133). For example, deep learning techniques have been used to predict PCa outcomes from multi-omics data, providing novel insights into tumor heterogeneity and treatment responses (101). The identification of specific AI frameworks that are able to integrate high-dimensional data, such as whole-genome sequencing and RNA expression profiles, will be key to the development of comprehensive predictive models that account for individual variations.

AI applications can also assist in the identification of novel biomarkers. For example, generative models can be trained to discover previously unknown relationships among different omics layers, thus revealing new avenues for therapeutic intervention (134). Targeting specific pathways implicated in PCa using these models may lead to the identification of potential drug targets and facilitate the development of targeted therapies. Collaborative efforts that merge AI expertise with multi-omics research are also essential to ensure these technologies are effectively applied to clinical challenges.

Studies of multi-omics in PCa have revealed several promising biomarkers that exhibit potential in the understanding and management of this disease (135). These include circulating tumor DNA, which is of particular interest due to the non-invasive method of sample collection and its ability to provide real-time insights into tumor dynamics and treatment responses, rendering it an invaluable tool for monitoring disease progression and therapy efficacy (136). Additionally, AR splice variants, particularly AR-V7, are emerging as critical indicators of resistance to ADTs, underscoring the necessity for personalized approaches to treatment (34). Furthermore, studies on the dysregulation of miRNAs, such as miR-145 (137) and the miR-221/222 cluster (138), have highlighted their role in tumorigenesis and their potential as therapeutic targets. These biomarkers not only reflect the intricate mechanisms of PCa biology but also create new avenues for innovative diagnostic and therapeutic strategies. Ongoing research into these biomarkers is essential for the development of tailored treatments to improve clinical outcomes in PCa.

The future of multi-omics research in PCa is poised for growth, embracing the tenets of precision medicine and leveraging advanced computational technologies. Clinical applications are likely become increasingly personalized and effective, guided by new insights derived from AI and collaborative research efforts. The validation of selected biomarkers and comprehensive study of the interplay between different omics layers is essential to ensure that findings are translated into actionable clinical practices. By further exploring the complexities of PCa using multi-omics, progress is being made in the tailoring of treatments to the disease and the individual patient, ultimately improving outcomes and quality of life for those affected by this prevalent malignancy.

9. Conclusion

Multi-omics approaches have advanced the understanding of PCa and associated diagnostic strategies by enabling the more precise identification of molecular subtypes and biomarkers. This approach is transformative as it not only aids the early

detection of PCa but also supports the development of personalized treatment strategies. In the future, the integration of multi-omics data holds great promise for improving patient management, tailoring therapeutic interventions and ultimately leading to improved clinical outcomes for patients with PCa. However, continued research in this field will be essential to fully realize the potential of these innovative methodologies.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

LY and XS made key contributions to the conception of the manuscript. YL and PS were responsible for literature searching and analysis. LY, XS and PS were responsible for drafting and writing the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Patel VL, Busch EL, Friebel TM, Cronin A, Leslie G, McGuffog L, Adlard J, Agata S, Agnarsson BA, Ahmed M, *et al*: Association of genomic domains in BRCA1 and BRCA2 with prostate cancer risk and aggressiveness. Cancer Res 80: 624-638, 2020.
3. Ziglioli F, Patera A, Isgrò G, Campobasso D, Guarino G and Maestroni U: Impact of modifiable lifestyle risk factors for prostate cancer prevention: A review of the literature. Front Oncol 13: 1203791, 2023.
4. Varaprasad GL, Gupta VK, Prasad K, Kim E, Tej MB, Mohanty P, Verma HK, Raju GSR, Bhaskar L and Huh YS: Recent advances and future perspectives in the therapeutics of prostate cancer. Exp Hematol Oncol 12: 80, 2023.
5. Wasim S, Lee SY and Kim J: Complexities of prostate cancer. Int J Mol Sci 23: 14257, 2022.
6. Catalona WJ: Screening for prostate cancer. Lancet 343: 1437, 1994.
7. Heijnsdijk EA, Wever EM, Auvinen A, Hugosson J, Ciatto S, Nelen V, Kwiatkowski M, Villers A, Páez A, Moss SM, *et al*: Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 367: 595-605, 2012.
8. Ma Y, Liu Z, Yu W, Huang H, Wang Y and Niu Y: Investigating high-risk factors, precise diagnosis, and treatment of castration-resistant prostate cancer (CRPC). Comb Chem High Throughput Screen 27: 2598-2608, 2023.
9. Cai M, Song XL, Li XA, Chen M, Guo J, Yang DH, Chen Z and Zhao SC: Current therapy and drug resistance in metastatic castration-resistant prostate cancer. Drug Resist Updat 68: 100962, 2023.
10. Zhang N, Kandalai S, Zhou X, Hossain F and Zheng Q: Applying multi-omics toward tumor microbiome research. Imeta 2: e73, 2023.
11. He X, Liu X, Zuo F, Shi H and Jing J: Artificial intelligence-based multi-omics analysis fuels cancer precision medicine. Semin Cancer Biol 88: 187-200, 2023.
12. Sato G, Shirai Y, Namba S, Edahiro R, Sonehara K, Hata T, Uemura M, Biobank Japan Project; Matsuda K, Doki Y, *et al*: Pan-cancer and cross-population genome-wide association studies dissect shared genetic backgrounds underlying carcinogenesis. Nat Commun 14: 3671, 2023.
13. Uo T, Sprenger CC and Plymate SR: Androgen receptor signaling and metabolic and cellular plasticity during progression to castration resistant prostate cancer. Front Oncol 10: 580617, 2020.
14. Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM, Montgomery B, Taplin ME, Pritchard CC, Attard G, *et al*: Integrative clinical genomics of advanced prostate cancer. Cell 161: 1215-1228, 2015.
15. Chi KN, Barnicle A, Sibilla C, Lai Z, Corcoran C, Barrett JC, Adelman CA, Qiu P, Easter A, Dearden S, *et al*: Detection of BRCA1, BRCA2, and ATM alterations in matched tumor tissue and circulating tumor DNA in patients with prostate cancer screened in PROfound. Clin Cancer Res 29: 81-91, 2023.
16. Wokołorczyk D, Kluźniak W, Stempa K, Rusak B, Huzarski T, Gronwald J, Gliniewicz K, Kashyap A, Morawska S, Dębniak T, *et al*: PALB2 mutations and prostate cancer risk and survival. Br J Cancer 125: 569-575, 2021.
17. Karlsson Q, Brook MN, Dadaev T, Wakerell S, Saunders EJ, Muir K, Neal DE, Giles GG, MacInnis RJ, Thibodeau SN, *et al*: Rare germline variants in ATM predispose to prostate cancer: A PRACTICAL consortium study. Eur Urol Oncol 4: 570-579, 2021.
18. Alorjani M, Aburub M, Al-Trad B, Hamad MA, AbuAlarja M, Bashir SA, Al-Batayneh K and Zoubi MA: The prevalence of CHEK1 and CHEK2 mutations in prostate cancer: A Retrospective cohort study. Med Arch 77: 8-12, 2023.
19. Sharma M, Yang Z and Miyamoto H: Loss of DNA mismatch repair proteins in prostate cancer. Medicine (Baltimore) 99: e20124, 2020.
20. Rusak B, Kluźniak W, Wokołorczykv D, Stempa K, Kashyap A, Gronwald J, Huzarski T, Dębniak T, Jakubowska A, Masojć B, *et al*: Inherited NBN mutations and prostate cancer risk and survival. Cancer Res Treat 51: 1180-1187, 2019.
21. Maxwell KN, Cheng HH, Powers J, Gulati R, Ledet EM, Morrison C, Le A, Hausler R, Stopfer J, Hyman S, *et al*: Inherited TP53 variants and risk of prostate cancer. Eur Urol 81: 243-250, 2022.
22. Imada EL, Sanchez DF, Dinalankara W, Vidotto T, Ebot EM, Tyekucheva S, Franco GR, Mucci LA, Loda M, Schaeffer EM, *et al*: Transcriptional landscape of PTEN loss in primary prostate cancer. BMC Cancer 21: 856, 2021.
23. Goldberg H, Spratt D, Chandrasekar T, Klaassen Z, Wallis CJD, Santiago-Jimenez M, Fishbane N, Davicioni E, Noorani R, Ahmad AE, *et al*: Clinical-genomic characterization unveils more aggressive disease features in elderly prostate cancer patients with low-grade disease. Eur Urol Focus 7: 797-806, 2021.
24. Ikeda S, Elkin SK, Tomson BN, Carter JL and Kurzrock R: Next-generation sequencing of prostate cancer: Genomic and pathway alterations, potential actionability patterns, and relative rate of use of clinical-grade testing. Cancer Biol Ther 20: 219-226, 2019.
25. Kalampokis N, Zabaftis C, Spinos T, Karavitakis M, Leotsakos I, Katafigiotis I, van der Poel H, Grivas N and Mitropoulos D: Review on the role of BRCA mutations in genomic screening and risk stratification of prostate cancer. Curr Oncol 31: 1162-1169, 2024.

26. He Y, Xu W, Xiao YT, Huang H, Gu D and Ren S: Targeting signaling pathways in prostate cancer: Mechanisms and clinical trials. Signal Transduct Target Ther 7: 198, 2022.
27. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, Chi KN, Sartor O, Agarwal N, Olmos D, *et al*: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382: 2091-2102, 2020.
28. Kulda V, Topolcan O, Kucera R, Kripnerova M, Srbecka K, Hora M, Hes O, Klecka J, Babuska V, Rousarova M, *et al*: Prognostic significance of TMPRSS2-ERG fusion gene in prostate cancer. Anticancer Res 36: 4787-4793, 2016.
29. Song C and Chen H: Predictive significance of TMRPSS2-ERG fusion in prostate cancer: A meta-analysis. Cancer Cell Int 18: 177, 2018.
30. Álvarez-Garcia V, Tawil Y, Wise HM and Leslie NR: Mechanisms of PTEN loss in cancer: It's all about diversity. Semin Cancer Biol 59: 66-79, 2019.
31. LaTulippe E, Satagopan J, Smith A, Scher H, Scardino P, Reuter V and Gerald WL: Comprehensive gene expression analysis of prostate cancer reveals distinct transcriptional programs associated with metastatic disease. Cancer Res 62: 4499-4506, 2002.
32. Itkonen HM, Urbanucci A, Martin SE, Khan A, Mathelier A, Thiede B, Walker S and Mills IG: High OGT activity is essential for MYC-driven proliferation of prostate cancer cells. Theranostics 9: 2183-2197, 2019.
33. Prensner JR, Chen W, Han S, Iyer MK, Cao Q, Kothari V, Evans JR, Knudsen KE, Paulsen MT, Ljungman M, *et al*: The long non-coding RNA PCAT-1 promotes prostate cancer cell proliferation through cMyc. Neoplasia 16: 900-908, 2014.
34. Yang Y, Lv G, Xiu R, Yang H, Wang W, Yu P, Zhang J, Ye L, Wang H and Tian J: Novel selective agents for the degradation of AR/AR-V7 to treat advanced prostate cancer. Eur J Med Chem 271: 116400, 2024.
35. de Wet L, Williams A, Gillard M, Kregel S, Lamperis S, Gutgesell LC, Vellky JE, Brown R, Conger K, Paner GP, *et al*: SOX2 mediates metabolic reprogramming of prostate cancer cells. Oncogene 41: 1190-1202, 2022.
36. Yi Q, Han X, Yu HG, Chen HY, Qiu D, Su J, Lin R, Batist G and Wu JH: SC912 inhibits AR-V7 activity in castration-resistant prostate cancer by targeting the androgen receptor N-terminal domain. Oncogene 43: 1522-1533, 2024.
37. Verma P, Shukla N, Kumari S, Ansari MS, Gautam NK and Patel GK: Cancer stem cell in prostate cancer progression, metastasis and therapy resistance. Biochim Biophys Acta Rev Cancer 1878: 188887, 2023.
38. Grimm D, Bauer J, Wise P, Krüger M, Simonsen U, Wehland M, Infanger M and Corydon TJ: The role of SOX family members in solid tumours and metastasis. Semin Cancer Biol 67 (Pt 1): 122-153, 2020.
39. Fu Q, Wang F, Yang J, Sun W, Hu Z, Xu L, Chu H, Wang X and Zhang W: Long non-coding RNA-PCGEM1 contributes to prostate cancer progression by sponging microRNA miR-129-5p to enhance chromatin licensing and DNA replication factor 1 expression. Bioengineered 13: 9411-9424, 2022.
40. Mu X, Shen Z, Lin Y, Xiao J, Xia K, Xu C, Chen B, Shi R, Zhu A, Sun X, *et al*: LncRNA-MALAT1 regulates cancer glucose metabolism in prostate cancer via MYBL2/mTOR axis. Oxid Med Cell Longev 2022: 8693259, 2022.
41. Lu X, Chen D, Yang F and Xing N: Quercetin inhibits epithelial-to-mesenchymal transition (EMT) process and promotes apoptosis in prostate cancer via downregulating lncRNA MALAT1. Cancer Manag Res 12: 1741-1750, 2020.
42. Zeng H, Huang Y, Liu Q, Liu H, Long T, Zhu C and Wu X: MiR-145 suppresses the motility of prostate cancer cells by targeting cadherin-2. Mol Cell Biochem 476: 3635-3646, 2021.
43. Gui B, Hsieh CL, Kantoff PW, Kibel AS and Jia L: Androgen receptor-mediated downregulation of microRNA-221 and -222 in castration-resistant prostate cancer. PLoS One 12: e0184166, 2017.
44. Ferreira M, Morais M, Medeiros R and Teixeira AL: MicroRNAs as promising therapeutic agents against prostate cancer resistant to castration-where are we now? Pharmaceutics 16: 1347, 2024.
45. Pungsrinont T, Kallenbach J and Baniahmad A: Role of PI3K-AKT-mTOR pathway as a pro-survival signaling and resistance-mediating mechanism to therapy of prostate cancer. Int J Mol Sci 22: 11088, 2021.
46. Eberlein C, Williamson SC, Hopcroft L, Ros S, Moss JI, Kerr J, van Weerden WM, de Bruin EC, Dunn S, Willis B, *et al*: Capivasertib combines with docetaxel to enhance anti-tumour activity through inhibition of AKT-mediated survival mechanisms in prostate cancer. Br J Cancer 130: 1377-1387, 2024.
47. Guan H, Liu C, Fang F, Huang Y, Tao T, Ling Z, You Z, Han X, Chen S, Xu B and Chen M: MicroRNA-744 promotes prostate cancer progression through aberrantly activating Wnt/β-catenin signaling. Oncotarget 8: 14693-14707, 2017.
48. Zhang K, Wu R, Mei F, Zhou Y, He L, Liu Y, Zhao X, You J, Liu B, Meng Q and Pei F: Phosphorylated $LASS_2$ inhibits prostate carcinogenesis via negative regulation of Wnt/β-catenin signaling. J Cell Biochem: Apr 14, 2021 (Epub ahead of print).
49. Marei HE, Hasan A, Pozzoli G and Cenciarelli C: Cancer immunotherapy with immune checkpoint inhibitors (ICIs): Potential, mechanisms of resistance, and strategies for reinvigorating T cell responsiveness when resistance is acquired. Cancer Cell Int 23: 64, 2023.
50. Jia D, Zhao M, Zhang X, Cheng X, Wei Q, Lou L, Zhao Y, Jin Q, Chen M and Zhang D: Transcriptomic analysis reveals the critical role of chemokine signaling in the anti-atherosclerosis effect of Xuefu Zhuyu decoction. J Ethnopharmacol 332: 118245, 2024.
51. Conley-LaComb MK, Saliganan A, Kandagatla P, Chen YQ, Cher ML and Chinni SR: PTEN loss mediated Akt activation promotes prostate tumor growth and metastasis via CXCL12/CXCR4 signaling. Mol Cancer 12: 85, 2013.
52. Hatano K and Nonomura N: Systemic therapies for metastatic castration-resistant prostate cancer: An updated review. World J Mens Health 41: 769-784, 2023.
53. de Kouchkovsky I, Rao A, Carneiro BA, Zhang L, Lewis C, Phone A, Small EJ, Friedlander T, Fong L, Paris PL, *et al*: A phase Ib/II study of the CDK4/6 inhibitor ribociclib in combination with docetaxel plus prednisone in metastatic castration-resistant prostate cancer. Clin Cancer Res 28: 1531-1539, 2022.
54. Agarwal N, Castellano D, Alonso-Gordoa T, Arranz Arija JA, Colomba E, Gravis G, Mourey L, Oudard S, Fléchon A, González M, *et al*: A signal-finding study of abemaciclib in heavily pretreated patients with metastatic castration-resistant prostate cancer: Results from CYCLONE 1. Clin Cancer Res 30: 2377-2383, 2024.
55. Tshering LF, Luo F, Russ S, Szenk M, Rubel D, Tutuska K, Rail JG, Balázsi G, Shen MM and Talos F: Immune mechanisms shape the clonal landscape during early progression of prostate cancer. Dev Cell 58: 1071-1086.e8, 2023.
56. Rebuzzi SE, Rescigno P, Catalano F, Mollica V, Vogl UM, Marandino L, Massari F, Pereira Mestre R, Zanardi E, Signori A, *et al*: Immune checkpoint inhibitors in advanced prostate cancer: Current data and future perspectives. Cancers (Basel) 14: 1245, 2022.
57. Shuken SR: An introduction to mass spectrometry-based proteomics. J Proteome Res 22: 2151-2171, 2023.
58. Al-Daffaie FM, Al-Mudhafar SF, Alhomsi A, Tarazi H, Almehdi AM, El-Huneidi W, Abu-Gharbieh E, Bustanji Y, Alqudah MAY, Abuhelwa AY, *et al*: Metabolomics and proteomics in prostate cancer research: Overview, analytical techniques, data analysis, and recent clinical applications. Int J Mol Sci 25: 5071, 2024.
59. Lee PY, Saraygord-Afshari N and Low TY: The evolution of two-dimensional gel electrophoresis - from proteomics to emerging alternative applications. J Chromatogr A 1615: 460763, 2020.
60. Zhu Y, Weiss T, Zhang Q, Sun R, Wang B, Yi X, Wu Z, Gao H, Cai X, Ruan G, *et al*: High-throughput proteomic analysis of FFPE tissue samples facilitates tumor stratification. Mol Oncol 13: 2305-2328, 2019.
61. Aurilio G, Cimadamore A, Mazzucchelli R, Lopez-Beltran A, Verri E, Scarpelli M, Massari F, Cheng L, Santoni M and Montironi R: Androgen receptor signaling pathway in prostate cancer: from genetics to clinical applications. Cells 9: 2653, 2020.
62. Dai C, Dehm SM and Sharifi N: Targeting the androgen signaling axis in prostate cancer. J Clin Oncol 41: 4267-4278, 2023.
63. Song Z, Zhou Q, Zhang JL, Ouyang J and Zhang ZY: Marker Ki-67 is a potential biomarker for the diagnosis and prognosis of prostate cancer based on two cohorts. World J Clin Cases 12: 32-41, 2024.
64. Xu L, Yin Y, Li Y, Chen X, Chang Y, Zhang H, Liu J, Beasley J, McCaw P, Zhang H, *et al*: A glutaminase isoform switch drives therapeutic resistance and disease progression of prostate cancer. Proc Natl Acad Sci USA 118: e2012748118, 2021.

65. Jiang B, Zhang J, Zhao G, Liu M, Hu J, Lin F, Wang J, Zhao W, Ma H, Zhang C, *et al*: Filamentous GLS1 promotes ROS-induced apoptosis upon glutamine deprivation via insufficient asparagine synthesis. Mol Cell 82: 1821-1835.e6, 2022.
66. Tampio J, Montaser AB, Järvinen J, Lehtonen M, Jalkanen AJ, Reinisalo M, Kokkola T, Terasaki T, Laakso M, Rysä J, *et al*: The L-type amino acid transporter 1 enhances drug delivery to the mouse pancreatic beta cell line (MIN6). Eur J Pharm Sci 203: 106937, 2024.
67. Chidley C, Darnell AM, Gaudio BL, Lien EC, Barbeau AM, Vander Heiden MG and Sorger PK: A CRISPRi/a screening platform to study cellular nutrient transport in diverse microenvironments. Nat Cell Biol 26: 825-838, 2024.
68. Xu M, Sakamoto S, Matsushima J, Kimura T, Ueda T, Mizokami A, Kanai Y and Ichikawa T: Up-regulation of LAT1 during antiandrogen therapy contributes to progression in prostate cancer cells. J Urol 195: 1588-1597, 2016.
69. Saito S, Ando K, Sakamoto S, Xu M, Yamada Y, Rii J, Kanaoka S, Wei J, Zhao X, Pae S, *et al*: The LAT1 inhibitor JPH203 suppresses the growth of castration-resistant prostate cancer through a CD24-mediated mechanism. Cancer Sci 115: 2461-2472, 2024.
70. Hoter A, Rizk S and Naim HY: The multiple roles and therapeutic potential of molecular chaperones in prostate cancer. Cancers (Basel 11: 1194, 2019.
71. Mori M, Hitora T, Nakamura O, Yamagami Y, Horie R, Nishimura H and Yamamoto T: Hsp90 inhibitor induces autophagy and apoptosis in osteosarcoma cells. Int J Oncol 46: 47-54, 2015.
72. Rastogi S, Joshi A, Sato N, Lee S, Lee MJ, Trepel JB and Neckers L: An update on the status of HSP90 inhibitors in cancer clinical trials. Cell Stress Chaperones 29: 519-539, 2024.
73. Tausif YM, Thekkekkara D, Sai TE, Jahagirdar V, Arjun HR, Meheronnisha HK, Babu A and Banerjee A: Heat shock protein paradigms in cancer progression: future therapeutic perspectives. 3 Biotech 14: 96, 2024.
74. Souza DS, Macheroni C, Pereira GJS, Vicente CM and Porto CS: Molecular regulation of prostate cancer by Galectin-3 and estrogen receptor. Front Endocrinol (Lausanne) 14: 1124111, 2023.
75. Keizman D, Frenkel M, Peer A, Rosenbaum E, Sarid D, Leibovitch I, Mano R, Yossepowitch O, Wolf I, Geva R, *et al*: Modified citrus pectin treatment in non-metastatic biochemically relapsed prostate cancer: Long-term results of a prospective phase II study. Nutrients 15: 3533, 2023.
76. Wang F, Li Z, Feng X, Yang D and Lin M: Advances in PSMA-targeted therapy for prostate cancer. Prostate Cancer Prostatic Dis 25: 11-26, 2022.
77. Yan Y, Zhuo H, Li T, Zhang J, Tan M and Chen Y: Advancements in PSMA ligand radiolabeling for diagnosis and treatment of prostate cancer: A systematic review. Front Oncol 14: 1373606, 2024.
78. Bakht MK and Beltran H: Biological determinants of PSMA expression, regulation and heterogeneity in prostate cancer. Nat Rev Urol 22: 26-45, 2025.
79. Fu P, Bu C, Cui B, Li N and Wu J: Screening of differentially expressed genes and identification of AMACR as a prognostic marker in prostate cancer. Andrologia 53: e14067, 2021.
80. Carswell BM, Woda BA, Wang X, Li C, Dresser K and Jiang Z: Detection of prostate cancer by alpha-methylacyl CoA racemase (P504S) in needle biopsy specimens previously reported as negative for malignancy. Histopathology 48: 668-673, 2006.
81. Quail DF and Walsh DA: Revolutionizing cancer research with spatial proteomics and visual intelligence. Nat Methods 21: 2216-2219, 2024.
82. Osmulski PA, Cunsolo A, Chen M, Qian Y, Lin CL, Hung CN, Mahalingam D, Kirma NB, Chen CL, Taverna JA, *et al*: Contacts with macrophages promote an aggressive nanomechanical phenotype of circulating tumor cells in prostate cancer. Cancer Res 81: 4110-4123, 2021.
83. Hsieh WC, Budiarto BR, Wang YF, Lin CY, Gwo MC, So DK, Tzeng YS and Chen SY: Spatial multi-omics analyses of the tumor immune microenvironment. J Biomed Sci 29: 96, 2022.
84. Kowalczyk T, Ciborowski M, Kisluk J, Kretowski A and Barbas C: Mass spectrometry based proteomics and metabolomics in personalized oncology. Biochim Biophys Acta Mol Basis Dis 1866: 165690, 2020.
85. Zhong AB, Muti IH, Eyles SJ, Vachet RW, Sikora KN, Bobst CE, Calligaris D, Stopka SA, Agar JN, Wu CL, *et al*: Multiplatform metabolomics studies of human cancers with NMR and mass spectrometry imaging. Front Mol Biosci 9: 785232, 2022.
86. Li R, Li L, Xu Y and Yang J: Machine learning meets omics: Applications and perspectives. Brief Bioinform 23: bbab460, 2022.
87. Ritterson Lew C, Guin S and Theodorescu D: Targeting glycogen metabolism in bladder cancer. Nat Rev Urol 12: 383-391, 2015.
88. Chetta P, Sriram R and Zadra G: Lactate as key metabolite in prostate cancer progression: What are the clinical implications? Cancers (Basel) 15: 3473, 2023.
89. Gatenby RA and Gillies RJ: Why do cancers have high aerobic glycolysis? Nat Rev Cancer 4: 891-899, 2004.
90. Chen L, Xu YX, Wang YS and Zhou JL: Lipid metabolism, amino acid metabolism, and prostate cancer: A crucial metabolic journey. Asian J Androl 26: 123-134, 2024.
91. Zeković M, Bumbaširević U, Živković M and Pejčić T: Alteration of lipid metabolism in prostate cancer: Multifaceted oncologic implications. Int J Mol Sci 24: 1391, 2023.
92. Škara L, Huđek Turković A, Pezelj I, Vrtarić A, Sinčić N, Krušlin B and Ulamec M: Prostate cancer-focus on cholesterol. Cancers (Basel) 13: 4696, 2021.
93. Yun SJ, Yan C, Jeong P, Kang HW, Kim YH, Kim EA, Lee OJ, Kim WT, Moon SK, Kim IY, *et al*: Comparison of mRNA, protein, and urinary nucleic acid levels of S100A8 and S100A9 between prostate cancer and BPH. Ann Surg Oncol 22: 2439-2445, 2015.
94. Srihari S, Kwong R, Tran K, Simpson R, Tattam P and Smith E: Metabolic deregulation in prostate cancer. Mol Omics 14: 320-329, 2018.
95. Singh R and Mills IG: The interplay between prostate cancer genomics, metabolism, and the epigenome: Perspectives and future prospects. Front Oncol 11: 704353, 2021.
96. Penney KL, Tyekucheva S, Rosenthal J, El Fandy H, Carelli R, Borgstein S, Zadra G, Fanelli GN, Stefanizzi L, Giunchi F, *et al*: Metabolomics of prostate cancer gleason score in tumor tissue and serum. Mol Cancer Res 19: 475-484, 2021.
97. Salciccia S, Capriotti AL, Laganà A, Fais S, Logozzi M, De Berardinis E, Busetto GM, Di Pierro GB, Ricciuti GP, Del Giudice F, *et al*: Biomarkers in prostate cancer diagnosis: from current knowledge to the role of metabolomics and exosomes. Int J Mol Sci 22: 4367, 2021.
98. Bansal N, Kumar M, Sankhwar SN and Gupta A: Evaluation of prostate cancer tissue metabolomics: Would clinics utilise it for diagnosis? Expert Rev Mol Med 25: e26, 2023.
99. Lima AR, Carvalho M, Aveiro SS, Melo T, Domingues MR, Macedo-Silva C, Coimbra N, Jerónimo C, Henrique R, Bastos ML, *et al*: Comprehensive metabolomics and lipidomics profiling of prostate cancer tissue reveals metabolic dysregulations associated with disease development. J Proteome Res 21: 727-739, 2022.
100. Sirocchi C, Bogliolo A and Montagna S: Medical-informed machine learning: Integrating prior knowledge into medical decision systems. BMC Med Inform Decis Mak 24 (Suppl 4): S186, 2024.
101. Yu X, Liu R, Gao W, Wang X and Zhang Y: Single-cell omics traces the heterogeneity of prostate cancer cells and the tumor microenvironment. Cell Mol Biol Lett 28: 38, 2023.
102. Murphy N, Shah P, Shih A, Khalili H, Liew A, Zhu X and Lee A: Single-cell sequencing in genitourinary malignancies. Adv Exp Med Biol 1255: 153-164, 2020.
103. Lu J, Sheng Y, Qian W, Pan M, Zhao X and Ge Q: scRNA-seq data analysis method to improve analysis performance. IET Nanobiotechnol 17: 246-256, 2023.
104. Song H, Weinstein HNW, Allegakoen P, Wadsworth MH II, Xie J, Yang H, Castro EA, Lu KL, Stohr BA, Feng FY, *et al*: Single-cell analysis of human primary prostate cancer reveals the heterogeneity of tumor-associated epithelial cell states. Nat Commun 13: 141, 2022.
105. Feng DC, Zhu WZ, Wang J, Li DX, Shi X, Xiong Q, You J, Han P, Qiu S, Wei Q and Yang L: The implications of single-cell RNA-seq analysis in prostate cancer: unraveling tumor heterogeneity, therapeutic implications and pathways towards personalized therapy. Mil Med Res 11: 21, 2024.
106. Amirifar L, Besanjideh M, Nasiri R, Shamloo A, Nasrollahi F, de Barros NR, Davoodi E, Erdem A, Mahmoodi M, Hosseini V, *et al*: Droplet-based microfluidics in biomedical applications. Biofabrication 14: 022001, 2022.
107. Xin S, Liu X, Li Z, Sun X, Wang R, Zhang Z, Feng X, Jin L, Li W, Tang C, *et al*: ScRNA-seq revealed an immunosuppression state and tumor microenvironment heterogeneity related to lymph node metastasis in prostate cancer. Exp Hematol Oncol 12: 49, 2023.

108. Peng G, Wang C, Wang H, Qu M, Dong K, Yu Y, Jiang Y, Gan S and Gao X: Gankyrin-mediated interaction between cancer cells and tumor-associated macrophages facilitates prostate cancer progression and androgen deprivation therapy resistance. Oncoimmunology 12: 2173422, 2023.
109. Mengistu BA, Tsegaw T, Demessie Y, Getnet K, Bitew AB, Kinde MZ, Beirhun AM, Mebratu AS, Mekasha YT, Feleke MG and Fenta MD: Comprehensive review of drug resistance in mammalian cancer stem cells: Implications for cancer therapy. Cancer Cell Int 24: 406, 2024.
110. Hu WY, Hu DP, Xie L, Nonn L, Lu R, Abern M, Shioda T and Prins GS: Keratin profiling by single-cell RNA-sequencing identifies human prostate stem cell lineage hierarchy and cancer stem-like cells. Int J Mol Sci 22: 8109, 2021.
111. Muller L, Fauvet F, Chassot C, Angileri F, Coutant A, Dégletagne C, Tonon L, Saintigny P, Puisieux A, Morel AP, *et al*: EMT-driven plasticity prospectively increases cell-cell variability to promote therapeutic adaptation in breast cancer. Cancer Cell Int 25: 32, 2025.
112. Wei G, Zhu H, Zhou Y, Pan Y, Yi B and Bai Y: Single-cell sequencing revealed metabolic reprogramming and its transcription factor regulatory network in prostate cancer. Transl Oncol 44: 101925, 2024.
113. Nguyen AD, Haines C, Price MJ, Dalton TE, Baëta CD, Hockenberry HA and Goodwin CR: Single-cell RNA sequencing comparison of the human metastatic prostate spine tumor microenvironment. STAR Protoc 5: 102805, 2024.
114. Zhang L, Lee M, Maslov AY, Montagna C, Vijg J and Dong X: Analyzing somatic mutations by single-cell whole-genome sequencing. Nat Protoc 19: 487-516, 2024.
115. Zheng K, Hai Y, Xi Y, Zhang Y, Liu Z, Chen W, Hu X, Zou X and Hao J: Integrative multi-omics analysis unveils stemness-associated molecular subtypes in prostate cancer and pan-cancer: Prognostic and therapeutic significance. J Transl Med 21: 789, 2023.
116. Nevedomskaya E and Haendler B: From omics to multi-omics approaches for in-depth analysis of the molecular mechanisms of prostate cancer. Int J Mol Sci 23: 6281, 2022.
117. Ren S, Li J, Dorado J, Sierra A, González-Díaz H, Duardo A and Shen B: From molecular mechanisms of prostate cancer to translational applications: Based on multi-omics fusion analysis and intelligent medicine. Health Inf Sci Syst 12: 6, 2023.
118. Zhu Q, Zhao X, Zhang Y, Li Y, Liu S, Han J, Sun Z, Wang C, Deng D, Wang S, *et al*: Single cell multi-omics reveal intra-cell-line heterogeneity across human cancer cell lines. Nat Commun 14: 8170, 2023.
119. Nabavizadeh A, Barkovich MJ, Mian A, Ngo V, Kazerooni AF and Villanueva-Meyer JE: Current state of pediatric neuro-oncology imaging, challenges and future directions. Neoplasia 37: 100886, 2023.
120. Huang J, Mao L, Lei Q and Guo AY: Bioinformatics tools and resources for cancer and application. Chin Med J (Engl) 137: 2052-2064, 2024.
121. Chakraborty S, Sharma G, Karmakar S and Banerjee S: Multi-OMICS approaches in cancer biology: New era in cancer therapy. Biochim Biophys Acta Mol Basis Dis 1870: 167120, 2024.
122. Zhou Y, Xiao X, Dong L, Tang C, Xiao G and Xu L: Cooperative integration of spatially resolved multi-omics data with COSMOS. Nat Commun 16: 27, 2025.
123. Mohr AE, Ortega-Santos CP, Whisner CM, Klein-Seetharaman J and Jasbi P: Navigating challenges and opportunities in multi-omics integration for personalized healthcare. Biomedicines 12: 1496, 2024.
124. Viana JN, Pilbeam C, Howard M, Scholz B, Ge Z, Fisser C, Mitchell I, Raman S and Leach J: Maintaining high-touch in high-tech digital health monitoring and multi-omics prognostication: ethical, equity, and societal considerations in precision health for palliative care. OMICS 27: 461-473, 2023.
125. Ramos-Lopez O, Martinez JA and Milagro FA: Holistic integration of omics tools for precision nutrition in health and disease. Nutrients 14: 4074, 2022.
126. Ahmed Z: Practicing precision medicine with intelligently integrative clinical and multi-omics data analysis. Hum Genomics 14: 35, 2020.
127. Messina C, Giunta EF, Signori A, Rebuzzi SE, Banna GL, Maniam A, Buti S, Cattrini C, Fornarini G, Bauckneht M, *et al*: Combining PARP inhibitors and androgen receptor signalling inhibitors in metastatic prostate cancer: A quantitative synthesis and meta-analysis. Eur Urol Oncol 7: 179-188, 2024.
128. Markowski MC, Sternberg CN, Wang H, Wang T, Linville L, Marshall CH, Sullivan R, King S, Lotan TL and Antonarakis ES: TRIUMPH: Phase II trial of rucaparib monotherapy in patients with metastatic hormone-sensitive prostate cancer harboring germline homologous recombination repair gene mutations. Oncologist 29: 794-800, 2024.
129. Gasmi A, Roubaud G, Dariane C, Barret E, Beauval JB, Brureau L, Créhange G, Fiard G, Fromont G, Gauthé M, *et al*: Overview of the development and use of akt inhibitors in prostate cancer. J Clin Med 11: 160, 2021.
130. Noori M, Azizi S, Mahjoubfar A, Abbasi Varaki F, Fayyaz F, Mousavian AH, Bashash D, Kardoust Parizi M and Kasaeian A: Efficacy and safety of immune checkpoint inhibitors for patients with prostate cancer: A systematic review and meta-analysis. Front Immunol 14: 1181051, 2023.
131. Wei Z, Han D, Zhang C, Wang S, Liu J, Chao F, Song Z and Chen G: Deep learning-based multi-omics integration robustly predicts relapse in prostate cancer. Front Oncol 12: 893424, 2022.
132. Sinha A, Huang V, Livingstone J, Wang J, Fox NS, Kurganovs N, Ignatchenko V, Fritsch K, Donmez N, Heisler LE, *et al*: The proteogenomic landscape of curable prostate cancer. Cancer Cell 35: 414-427.e6, 2019.
133. Ozaki Y, Broughton P, Abdollahi H, Valafar H and Blenda AV: Integrating omics data and AI for cancer diagnosis and prognosis. Cancers (Basel) 16: 2448, 2024.
134. Baydoun A, Jia AY, Zaorsky NG, Kashani R, Rao S, Shoag JE, Vince RA Jr, Bittencourt LK, Zuhour R, Price AT, *et al*: Artificial intelligence applications in prostate cancer. Prostate Cancer Prostatic Dis 27: 37-45, 2024.
135. Bian X, Wang W, Abudurexiti M, Zhang X, Ma W, Shi G, Du L, Xu M, Wang X, Tan C, *et al*: Integration analysis of single-cell multi-omics reveals prostate cancer heterogeneity. Adv Sci (Weinh) 11: e2305724, 2024.
136. Fonseca NM, Maurice-Dror C, Herberts C, Tu W, Fan W, Murtha AJ, Kollmannsberger C, Kwan EM, Parekh K, Schönlau E, *et al*: Prediction of plasma ctDNA fraction and prognostic implications of liquid biopsy in advanced prostate cancer. Nat Commun 15: 1828, 2024.
137. Armstrong L, Willoughby CE and McKenna DJ: The suppression of the epithelial to mesenchymal transition in prostate cancer through the targeting of MYO6 Using MiR-145-5p. Int J Mol Sci 25: 4301, 2024.
138. Yu B, Zuo X and Zhao C: Efficacy of abiraterone combined with prednisone in castration-resistant prostate cancer and its impact on miR-221/222 expression. Am J Cancer Res 14: 4708-4716, 2024.