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Genetic Mutations in Prostate Cancer: Insights and Implications

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Abstract

This review article aims to provide a comprehensive overview of genetic mutations and alterations in prostate cancer, highlighting their roles in disease development and progression. The scope of the review encompasses common genetic mutations, such as those in the PTEN and TP53 genes, as well as structural alterations like the TMPRSS2-ERG fusion. It also discusses the impact of these genetic changes on cellular functions, including cell cycle regulation and signaling pathways. Major findings indicate that genetic mutations contribute to the uncontrolled proliferation of prostate cells and influence treatment responses, emphasizing the importance of molecular profiling in guiding personalized therapy. Additionally, the review explores the significance of the tumor microenvironment and epigenetic modifications in prostate cancer progression. The insights gained from this review underscore the necessity for ongoing research into genetic alterations to improve diagnostic methods and therapeutic strategies, ultimately enhancing patient outcomes.

Keywords: Prostate cancer; Genetic mutations; PTEN; TMPRSS2-ERG fusion; Personalized therapy; Tumor microenvironment

1. Introduction

1.1. Overview of Molecular Mechanism of Prostate Cancer

Cancer is fundamentally a genetic disease characterized by uncontrolled cell proliferation and survival of damaged cells (1). Prostate cancer is particularly notable, being the second most common cancer among men worldwide, with an estimated 1.4 million new cases diagnosed in 2020 alone (2). The prostate gland, a small walnut-shaped organ located below the bladder and in front of the rectum, is primarily affected by this disease (3).

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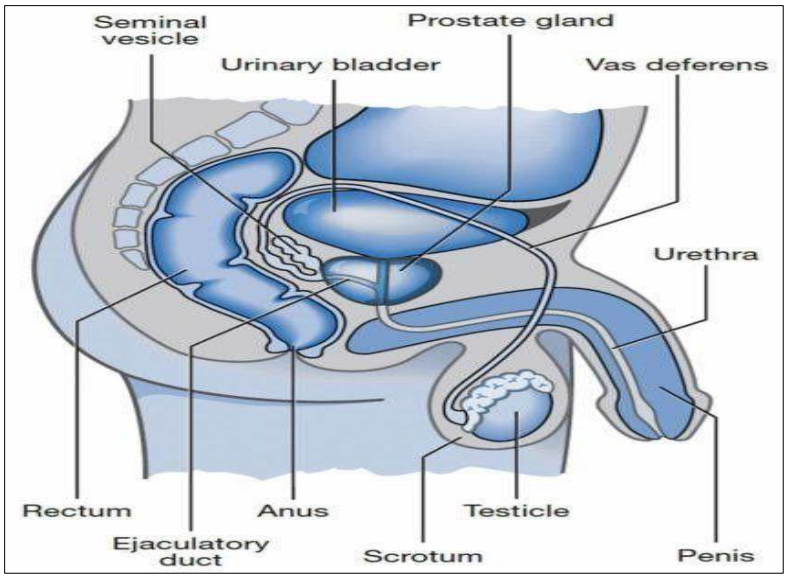
1.2. Epidemiology of Prostate Cancer

The epidemiology of prostate cancer reveals significant variations in incidence and mortality rates across different demographics. In the United States, prostate cancer is the most frequently diagnosed cancer among men, accounting for approximately 20% of all new cancer cases (4). The lifetime risk of being diagnosed with prostate cancer is about 1 in 8, with the risk increasing significantly with age. The median age at diagnosis is around 66 years, and the majority of cases are diagnosed in men aged 65 and older (5). Globally, the incidence of prostate cancer varies widely, with the highest rates observed in North America and Western Europe. For instance, in 2020, the age-standardized incidence rate was reported to be 118.6 per 100,000 men in the United States, compared to 30.0 per 100,000 in East Asia (2). This disparity is attributed to a combination of genetic, environmental, and lifestyle factors, as well as differences in screening practices and healthcare access. Mortality rates also exhibit significant demographic disparities. In the United States, prostate cancer is the second leading cause of cancer-related death among men, with an estimated 34,700 deaths in 2023 (4). The mortality rate is higher among African American men, who are 1.7 times more likely to die from prostate cancer compared to white men (6). This increased risk is thought to be influenced by a combination of genetic predisposition, socioeconomic factors, and access to healthcare. *Biological Significance of the Prostate Gland* The prostate gland plays a crucial role in male reproductive health. It is responsible for producing prostatic fluid, a key component of semen that nourishes and transports sperm during ejaculation. Prostatic fluid contains enzymes, citric acid, and other substances that enhance sperm motility and viability (7). The prostate also contributes to the regulation of testosterone levels, which are vital for the development and maintenance of male reproductive tissues. Normal prostate function is regulated by androgens, particularly testosterone and dihydrotestosterone (DHT). These hormones influence prostate development, growth, and secretory activities through androgen receptor (AR) signaling pathways (8). The balance of androgen signaling is essential for maintaining normal prostate function; however, dysregulation of this signaling can lead to pathological conditions, including benign prostatic hyperplasia (BPH) and prostate cancer. Prostate cancer disrupts the normal physiological functions of the prostate gland. As cancer cells proliferate uncontrollably, they can invade surrounding tissues and metastasize to distant sites, leading to significant morbidity and mortality. The presence of prostate cancer can also affect urinary function, sexual health, and overall quality of life for affected individuals (9). Understanding the biological significance of the prostate gland and the impact of prostate cancer on its functions is essential for developing effective prevention and treatment strategies. Recent advancements in molecular markers and imaging techniques have transformed prostate cancer screening, diagnosis, and treatment (10). Genetic mutations, defined as changes in nucleotide sequences within the genome, play a critical role in cancer development(11). These mutations can lead to alterations in gene function and observable changes in phenotype (12). Various types of mutations, including point mutations, chromosomal mutations, and copy number variations, contribute to the genomic instability characteristic of prostate cancer (13). Understanding these genetic alterations is essential for developing targeted therapies and improving patient outcomes.



Source: https://www.prostate-cancer-support-geelong.net/what-is-the-prostate.

Figure 1 Anatomy of prostate gland

2. Overview of Common Genetic Mutations and Alterations in Prostate Cancer

Common Genetic Mutations in Prostate Cancer Prostate cancer is characterized by a variety of genetic mutations that contribute to its development and progression. While mutations in the *Phosphate and Tension Homolog Gene (PTEN)and Tumor Protein 53 (TP53)* are well-established, several other critical genes are also implicated in prostate cancer pathogenesis.

2.1. Loss of Phosphate and Tension Homolog Gene (PTEN)

PTEN is a crucial tumor suppressor gene located on chromosome 10q23, encoding a dual specificity protein that inhibits cell growth and promotes apoptosis (14). PTEN functions by downregulating the phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling pathway, which is frequently upregulated in cancer. Mutations or deletions in PTEN lead to enhanced cell proliferation and survival, contributing to tumorigenesis (14).

2.2. Tumor Protein 53 (TP53) Mutation

TP53, located on chromosome 17p13.1, encodes the p53 protein, a critical regulator of the cell cycle, DNA repair, and apoptosis (15). Mutations in TP53 are common in prostate cancer and often result from chromosomal deletions. Loss of p53 function impairs genomic stability and promotes tumor progression (16).

2.3. Androgen Receptor (AR) Mutations

The androgen receptor (AR) gene, located on the X chromosome, is a key player in prostate cancer. Mutations in the AR gene can lead to constitutive activation of the receptor, even in the absence of androgens, which promotes tumor growth and progression(8). AR mutations are particularly associated with castration-resistant prostate cancer (CRPC), where tumors continue to grow despite androgen deprivation therapy(17) . These mutations often enhance the receptor's transcriptional activity, leading to increased expression of genes that promote cell proliferation and survival.

2.4. BRCA1 and BRCA2 Mutations

Mutations in the BRCA1 and BRCA2 genes, which are primarily known for their role in breast and ovarian cancer, have also been implicated in prostate cancer. Men with BRCA2 mutations have a significantly increased risk of developing prostate cancer, particularly aggressive forms of the disease(18) . BRCA1/2 are involved in DNA repair through homologous recombination, and mutations in these genes can lead to genomic instability, accumulation of mutations, and ultimately carcinogenesis (19).

2.5. Other Notable Genetic Alterations

ETV1, ETV4, and ETV5: These genes belong to the ETS family of transcription factors and are often involved in gene fusions with TMPRSS2 in prostate cancer. The TMPRSS2-ERG fusion is the most common, leading to overexpression of ERG, which promotes cell proliferation and invasion (20).

- *ARID1A:* Mutations in the ARID1A gene, which is involved in chromatin remodeling, have been associated with prostate cancer. Loss of ARID1A function can lead to altered gene expression profiles that favor tumorigenesis (21).
- *SPOP:* Mutations in the SPOP gene, which encodes a substrate recognition component of an E3 ubiquitin ligase, are frequently found in prostate cancer. These mutations can disrupt the degradation of oncogenic proteins, contributing to tumor growth (22).

2.6. Mechanisms of Carcinogenesis

The mechanisms by which these genetic mutations contribute to carcinogenesis in prostate cancer are multifaceted:

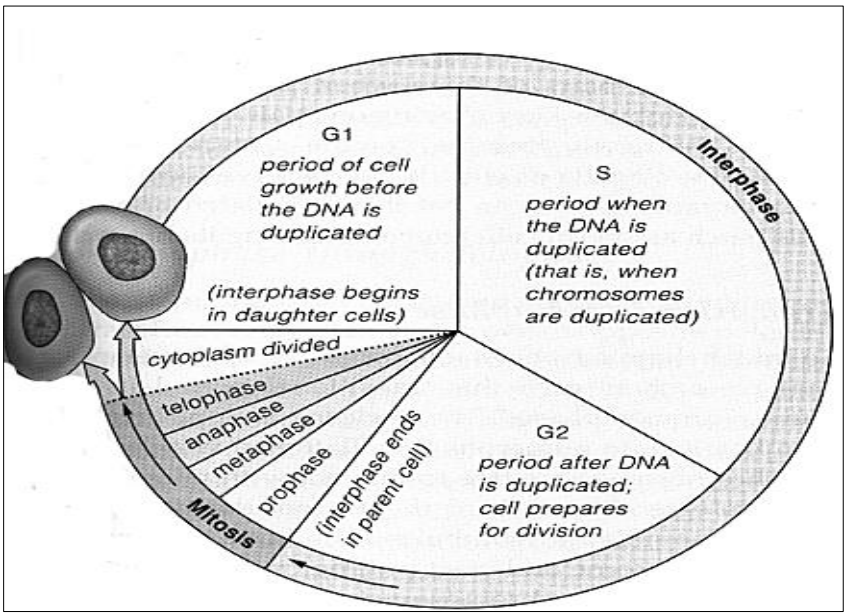
- *Disruption of Tumor Suppressor Function*: Mutations in tumor suppressor genes like PTEN and TP53 lead to the loss of regulatory control over cell growth and survival. This loss allows for unchecked cell proliferation and the accumulation of additional mutations, promoting tumorigenesis(16).
- *Constitutive Activation of Oncogenes:* Mutations in the AR gene can lead to constitutive activation of the androgen receptor, promoting the expression of genes that drive cell proliferation and survival, even in low androgen environments. This is particularly relevant in the context of CRPC, where tumors adapt to androgen deprivation(23).

- *Genomic Instability*: Mutations in BRCA1 and BRCA2 impair DNA repair mechanisms, leading to increased genomic instability. This instability results in the accumulation of further mutations that can drive cancer progression(19).
- *Altered Gene Expression:* Fusions such as TMPRSS2-ERG lead to the overexpression of oncogenic transcription factors, which can alter the expression of multiple downstream target genes involved in cell cycle regulation, apoptosis, and invasion (24).
- *Disruption of Cellular Signaling Pathways:* Mutations in genes like SPOP can disrupt normal cellular signaling pathways, leading to enhanced survival and proliferation of cancer cells (22).

Understanding these genetic mutations and their mechanisms is crucial for developing targeted therapies and improving patient outcomes in prostate cancer.

3. Cell cycle and oncogenetics of prostate cancer

The cell cycle comprises a series of events leading to cell division and replication. It consists of four phases: G1 (gap 1), S (synthesis), G2 (gap 2), and M (mitosis) (25). Progression through these phases is tightly regulated by cyclin-dependent kinases (CDKs) and their regulatory cyclins, ensuring genomic integrity and balanced cell growth (26).



Source: Cell Cycle. (n.d.). RetrievedOctober6,2024, from https://www.researchgate.net/publication/295918233_Cell Cycle

Figure 2 The cell cycle

3.1. Molecular Mechanisms of Cell Cycle Regulation

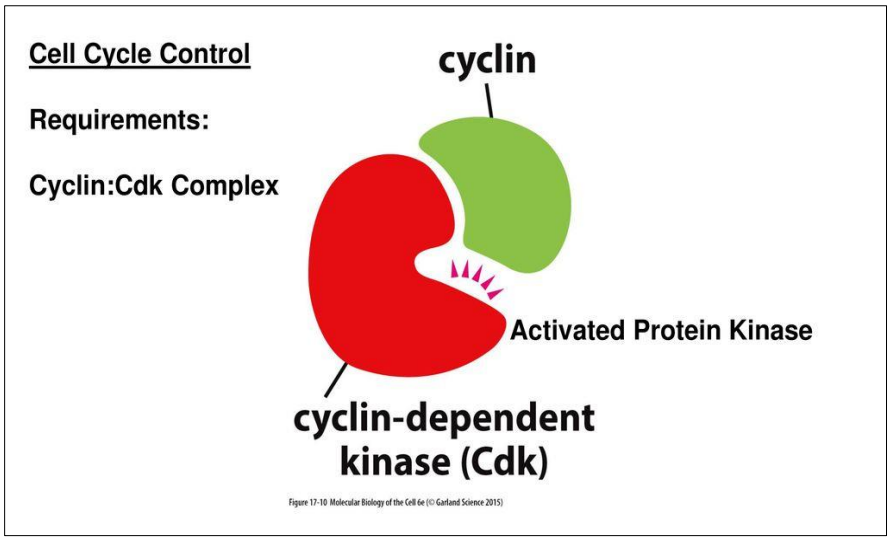
Cell cycle regulation is a complex process that involves a series of checkpoints and signaling pathways that ensure the proper timing and order of cell division. Key players in this regulation are cyclins and CDKs, which form cyclin-CDK complexes that drive the cell cycle forward.

3.1.1. Cyclin-Dependent Kinases (CDKs)

CDKs are serine/threonine kinases that, when activated by binding to cyclins, phosphorylate target proteins to promote cell cycle progression. *CDK4 and CDK6*: These kinases are primarily involved in the transition from the G1 phase to the S phase. They form complexes with cyclin D, which is crucial for the phosphorylation of the retinoblastoma protein (Rb). Phosphorylation of Rb releases E2F transcription factors, allowing the expression of genes necessary for DNA synthesis (15).

- *CDK2*: This kinase is active during the S phase and G2 phase. It forms complexes with cyclin E and cyclin A, facilitating DNA replication and preparing the cell for mitosis (27).
- CDK1: Also known as cyclin-dependent kinase 1, it is essential for the transition from G2 to M phase. CDK1 forms a complex with cyclin B, which is critical for the initiation of mitosis(28).

- *Cyclins*: Cyclins are regulatory proteins whose levels fluctuate throughout the cell cycle. They activate CDKs by forming cyclin-CDK complexes.
- *Cyclin D*: This cyclin is crucial for the G1 phase and is regulated by growth factors. Its expression is often upregulated in prostate cancer, leading to increased CDK4/6 activity and promoting cell cycle progression (29).
- *Cyclin E*: This cyclin is involved in the G1/S transition and is often overexpressed in various cancers, including prostate cancer, contributing to uncontrolled cell proliferation (30) .
- *Cyclin A:* Active during the S phase and G2 phase, cyclin A is essential for DNA replication and mitotic entry(30) .

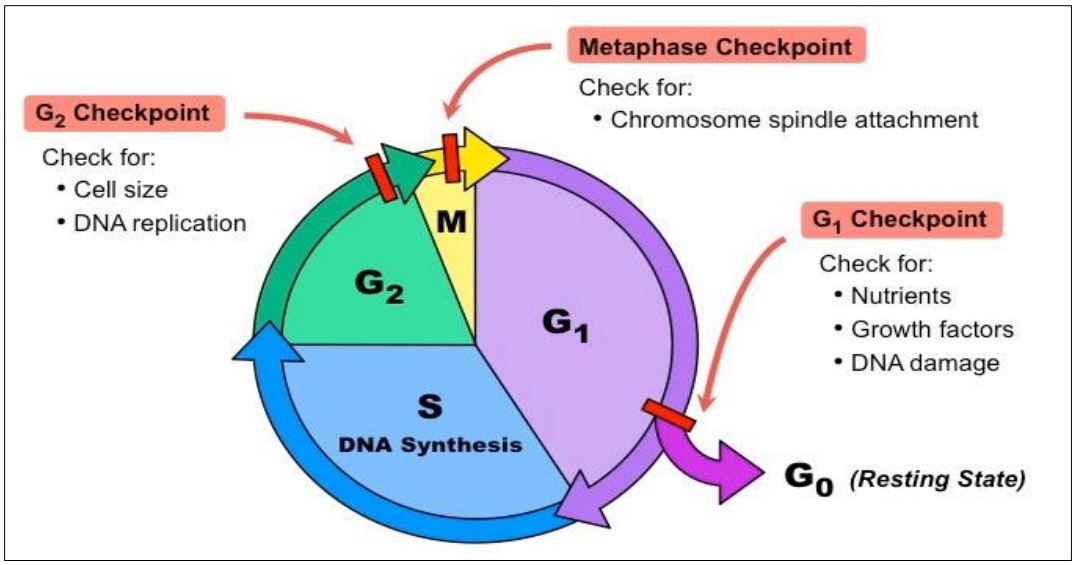


Source: https://praxilabs.com/en/blog/2021/07/06/cell-cycle-regulation-en/

Figure 3 Interaction between cyclin and cyclin-dependent kinase (CDK) in cell cycle

Cell Cycle Checkpoints Cell cycle checkpoints are critical control mechanisms that monitor the integrity of the genome and ensure that cells do not proceed to the next phase of the cycle if DNA damage is detected. The main checkpoints include:

- *G1/S Checkpoint*: This checkpoint assesses DNA integrity and the cell's readiness for DNA synthesis. If DNA damage is detected, the cell cycle is halted, allowing for repair mechanisms to be activated. If the damage is irreparable, apoptosis may be triggered (31).
- *G2/M Checkpoint*: This checkpoint ensures that DNA replication has been completed successfully and that the cell is ready to enter mitosis. It prevents cells with damaged DNA from undergoing mitosis (32).
- *Spindle Assembly Checkpoint*: This checkpoint ensures that all chromosomes are properly attached to the mitotic spindle before allowing the cell to proceed with mitosis.



Source: Cell Checkpoints | BioNinja. (n.d.). Retrieved October 6, 2024, from https://old-ib.bioninja.com.au/standard-level/topic-1-cell-biology/16-cell-division/cell-checkpoints.html

Figure 4 Cell Checkpoints

Dysregulation of Cell Cycle Pathways and Cancer Dysregulation of cell cycle pathways can lead to uncontrolled cell proliferation and tumor formation. In prostate cancer, several mechanisms contribute to this dysregulation:

- *Mutations in Tumor Suppressor Genes*: Mutations in genes such as TP53 and PTEN can disrupt the normal function of cell cycle checkpoints. For instance, loss of TP53 function impairs the G1/S checkpoint, allowing cells with damaged DNA to continue dividing (16).
- *Overexpression of Cyclins and CDKs*: Overexpression of cyclin D and CDK4/6 is common in prostate cancer, leading to enhanced phosphorylation of Rb and increased E2F activity, promoting cell cycle progression even in the presence of DNA damage(30). This aberrant signaling can lead to aggressive tumor behavior and resistance to therapy.
- *Alterations in CDK Inhibitors:* CDK inhibitors, such as p16INK4a, normally function to inhibit CDK4/6 activity. Loss of these inhibitors can lead to unchecked CDK activity and progression through the cell cycle (30).
- *Androgen Receptor Signaling:* The androgen receptor (AR) is a critical driver of prostate cancer. Dysregulation of AR signaling can enhance the expression of cyclins and CDKs, further promoting cell cycle progression and tumor growth(8).

4. Factors affecting genetic alterations and genetic mutations

Signaling Pathways and Their Influence on Genetic Alterations and Mutation The development and progression of prostate cancer are influenced by various signaling pathways that regulate cellular processes such as proliferation, survival, and differentiation. These pathways can be affected by environmental factors and lifestyle choices, which may contribute to genetic mutations and alterations.

- *Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/Akt) Pathway* The PI3K/Akt pathway is frequently activated in prostate cancer, promoting cell survival and proliferation (32). PTEN acts as a negative regulator of this pathway, and its loss leads to increased Akt activation, contributing to tumor growth. Environmental factors such as obesity and insulin resistance can activate this pathway, further promoting cancer progression(33).
- *Androgen Receptor Signaling Pathway* The androgen receptor (AR) is a critical driver of prostate cancer. Aberrant AR signaling, often due to mutations or overexpression, enhances tumor growth and progression (34). Lifestyle factors such as diet and physical activity can influence androgen levels and AR signaling. For instance, high-fat diets have been associated with increased levels of circulating androgens, which may enhance AR signaling and promote prostate cancer development (8). Additionally, AR splice variants can contribute to castration-resistant prostate cancer (CRPC) by promoting androgen-independent signaling.
- *Wnt Signaling Pathway* The Wnt signaling pathway is involved in cell proliferation and differentiation. Dysregulation of this pathway, often through mutations in β-catenin, has been implicated in prostate cancer

progression (35). Environmental factors such as exposure to certain chemicals (e.g., pesticides) may disrupt Wnt signaling, leading to increased risk of prostate cancer (36).

- *Nuclear Factor Kappa B (NF-κB) Pathway* The NF-κB pathway regulates inflammation and cell survival. Aberrant activation of NF-κB in prostate cancer promotes tumor growth and resistance to therapy (37). Chronic inflammation, often due to lifestyle factors such as smoking and obesity, can lead to persistent NF-κB activation, contributing to tumorigenesis (38).
- *Tumor Microenvironment* The tumor microenvironment (TME) comprises various cellular and non-cellular components that interact with tumor cells, influencing cancer progression(39). In prostate cancer, immune cells, stromal cells, and extracellular matrix components contribute to tumor development and therapeutic resistance(40).AR signaling can modulate immune responses within the TME, promoting an immunosuppressive environment that facilitates tumor evasion from immune surveillance. Environmental factors such as chronic inflammation and the presence of certain cytokines can further alter the TME, enhancing tumor growth and metastasis (41).

Environmental Factors and Lifestyle Choices Environmental factors and lifestyle choices play a significant role in the development of genetic mutations and alterations in prostate cancer. Key factors include:

- *Diet:* Diets high in saturated fats and low in fruits and vegetables have been associated with an increased risk of prostate cancer. Certain dietary components can influence hormone levels and signaling pathways, such as the AR pathway, leading to increased cancer risk (42).
- *Physical Activity:* Regular physical activity has been shown to reduce the risk of prostate cancer. Exercise can help regulate hormone levels, reduce inflammation, and improve immune function, all of which may contribute to lower cancer risk(6).
- *Obesity*: Obesity is a significant risk factor for prostate cancer and is associated with alterations in insulin signaling and inflammation. Increased adipose tissue can lead to elevated levels of circulating insulin and insulin-like growth factors, which can activate the PI3K/Akt pathway and promote tumor growth (43).
- *Smoking:* Tobacco use has been linked to various cancers, including prostate cancer. Smoking can induce genetic mutations and promote inflammation, contributing to tumorigenesis (35).
- *Chemical Exposures:* Exposure to certain environmental toxins, such as pesticides and industrial chemicals, has been associated with an increased risk of prostate cancer. These chemicals can disrupt normal cellular signaling pathways, leading to genetic alterations (44).

5. Future directions and research opportunities in studying genetic alterations and mutations

Future research in prostate cancer should prioritize the identification of novel genetic alterations, the characterization of their functional consequences, and the discovery of reliable biomarkers for diagnosis and treatment response. Integrating multi-omics approaches can provide a comprehensive understanding of prostate cancer biology and facilitate the development of targeted therapies (16). Below, we explore ongoing research initiatives, potential new biomarkers, therapeutic targets, and the role of precision medicine in prostate cancer treatment.

5.1. Ongoing Research in Genetic Alterations and Mutations

- *Identification of Novel Genetic Alterations*: Researchers are employing advanced genomic sequencing techniques, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS), to uncover previously unrecognized mutations and alterations in prostate cancer. These studies aim to elucidate the genetic landscape of prostate cancer and identify novel actionable mutations (45). Recent studies have highlighted the importance of non-coding RNA alterations, including microRNAs and long non-coding RNAs, which may play critical roles in tumorigenesis and progression(46).
- *Characterization of Functional Consequences:* Functional genomics approaches, including CRISPR/Cas9 gene editing, are being utilized to investigate the roles of specific mutations in prostate cancer. By creating knockout models, researchers can assess the impact of individual genetic alterations on cell proliferation, apoptosis, and response to therapy (47). Investigating the effects of these alterations on signaling pathways and cellular behavior can provide insights into tumor biology and potential therapeutic vulnerabilities.
- *Discovery of Reliable Biomarkers*: Biomarkers that predict treatment response and disease progression are critical for personalized medicine. Current research is focused on identifying circulating tumor DNA (ctDNA) and other liquid biopsy markers that can provide real-time insights into tumor dynamics and treatment efficacy(48).

  Emerging biomarkers, such as the expression levels of specific microRNAs and the presence of genetic

alterations in genes like AR, BRCA1/2, and others, are being explored for their potential to guide therapy decisions(9).

5.2. Therapeutic Targets and Precision Medicine

- *Targeting Novel Pathways*: Ongoing research is identifying new therapeutic targets beyond traditional pathways. For example, targeting the Wnt/β-catenin pathway, which is often dysregulated in prostate cancer, is an area of active investigation (19). Additionally, the development of inhibitors targeting the epigenetic landscape of prostate cancer, such as histone deacetylase (HDAC) inhibitors, is being explored as a means to reverse aberrant gene expression patterns (28).
- *Role of Precision Medicine*: Precision medicine in prostate cancer aims to tailor treatment based on individual genetic profiles. Ongoing clinical trials are evaluating the efficacy of targeted therapies based on specific genetic alterations, such as PARP inhibitors for patients with BRCA mutations and PI3K inhibitors for those with PTEN loss(19).The integration of genomic profiling into clinical practice is essential for identifying patients who are most likely to benefit from targeted therapies, thereby improving treatment outcomes and minimizing unnecessary side effects(49).

5.3. Implications of New Technologies

- *CRISPR Technology*: CRISPR/Cas9 technology is revolutionizing prostate cancer research by enabling precise editing of the genome. This technology allows researchers to create models that mimic the genetic alterations found in human tumors, facilitating the study of their functional consequences and potential therapeutic targets (47). CRISPR is also being explored for therapeutic applications, such as correcting mutations in tumor suppressor genes or enhancing the immune response against prostate cancer cells(50).
- *Advanced Genomic Sequencing:* Next-generation sequencing (NGS) technologies are providing deeper insights into the genetic landscape of prostate cancer. These technologies allow for the simultaneous analysis of multiple genes and pathways, facilitating the identification of co-occurring mutations and potential synergistic therapeutic targets (51). The integration of multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, can provide a holistic view of tumor biology and help identify novel biomarkers and therapeutic strategies(16).

5.4. Future Research Directions

- *Investigation of Novel Biomarkers Action*: Future research should focus on identifying and validating novel biomarkers that can predict treatment response and disease progression in prostate cancer.
- *Rationale*: Biomarkers can guide personalized treatment strategies and improve patient outcomes by allowing for more precise targeting of therapies.
- *Exploration of Combination Therapies*: *Action*: Research should explore the efficacy of combination therapies that target multiple pathways simultaneously, particularly in patients with complex genetic profiles.
- *Rationale*: Combination therapies may help overcome resistance mechanisms and enhance treatment efficacy, particularly in advanced disease settings.
- *Longitudinal Studies*: Action: Conduct longitudinal studies to assess the long-term outcomes of patients undergoing genetic testing and targeted therapies.
- Rationale: Understanding the long-term implications of genetic alterations and treatment responses will inform clinical practice and improve management strategies for prostate cancer.
- *Integration of Multi-Omics Approaches*: Action: Future studies should integrate multi-omics approaches (genomics, transcriptomics, proteomics) to provide a comprehensive understanding of prostate cancer biology.
- Rationale: This holistic view can uncover new therapeutic targets and enhance the development of personalized treatment strategies.

6. Conclusion

In summary, the evolving landscape of prostate cancer research highlights the critical role of genetic mutations and alterations in disease progression and treatment response. By implementing targeted recommendations for clinical practice, public health initiatives, and future research directions, we can improve early detection, enhance personalized treatment strategies, and ultimately improve outcomes for patients with prostate cancer. The integration of genetic insights into clinical decision-making will be essential for advancing the field and providing optimal care for patients.

Compliance with ethical standards

Disclosure of conflict of interest

The authors of this review paper declared no conflict of interest.

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