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A Systematic Review on the Intricate Epigenetic Landscape of Prostate Cancer: Navigating Molecular Complexities for Therapeutic Insights

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Abstract

Background: This comprehensive review investigates the expanding landscape of cancer genetics, with a specific focus on the escalating burden of prostate cancer in Bangladesh. Against the backdrop of increasing cancer prevalence and mortality rates in the country, particularly noteworthy in the case of prostate cancer.

Objectives: The study aims to unravel the genetic intricacies underpinning this complex disease. By exploring the genetic associations, signaling pathways, and variations related to prostate cancer, including the crucial role of the androgen receptor (AR), the research seeks to unravel critical insights into the disease's development and progression.

Methods: The study authors systematically reviewed literature databases, including but not limited to PubMed, Research Gate, Google scholar, PMC free article to identify studies that addressed the genetic and epigenetic factors influencing cancer development, progression, and treatment.

Results: In delving into the genetic intricacies of prostate cancer, the study sheds light on key players, such as the androgen receptor (AR), emphasizing its pivotal role in disease progression. Genetic variations in AR, including amplification, mutations, and splice variants like AR-V7, emerge as critical factors influencing prostate cancer development and resistance to androgen deprivation therapy (ADT). Additionally, the review unravels the broader genetic landscape, encompassing alterations in genes like BRCA1, BRCA2, and HOXB13, and dysregulation of signaling pathways like PI3K/AKT/mTOR.

Furthermore, the review examines the broader implications of these genetic findings, highlighting their significance in precision medicine, early detection, and the development of innovative therapies. As genetic aberrations take center stage in the understanding of cancer, the study emphasizes the need for continued research to refine treatment strategies and propel personalized approaches.

Conclusions: By synthesizing recent discoveries and emerging trends, the research serves as a valuable resource for researchers, clinicians, and students invested in unraveling the genetic tapestry of cancer, providing a platform for advancements in diagnosis, treatment, and the ongoing battle against this formidable adversary.

Keywords: Androgen Receptor, Cancer Epidemiology, Genetic Variations, Precision Medicine, Prostate Cancer

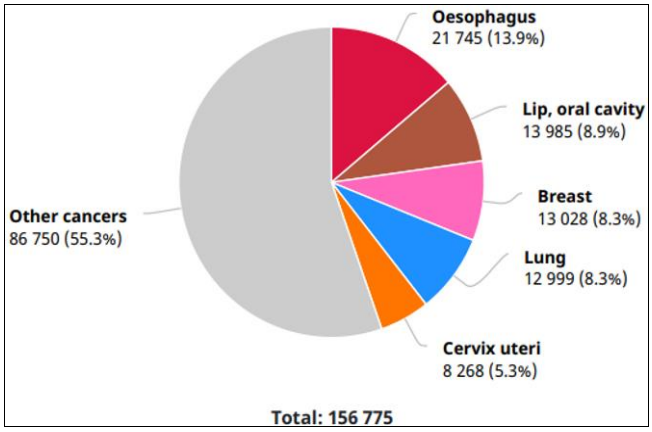
1. Background

Cancer is a complex and multifaceted group of diseases that pose a significant global health challenge. Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs [1]. The process of metastasizing, wherein cancer cells spread to other parts of the body, is a major cause of death from cancer [2]. A neoplasm and malignant tumour are other common names for cancer.

Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or 1 in 6 deaths, in 2018. Lung, prostate, colorectal, stomach, prostrate and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common among women [1].

The incidence and mortality rates of cancer in Bangladesh have shown a noteworthy increase. With a total population of 164,689,383, the country has experienced 156,775 new cancer cases and 108,990 deaths in 2020 [3]. The prevalence of cancer

cases over a five-year span stands at 270,866, indicating a substantial burden on the healthcare system.



Source: IARC, 2021

Fig 1: Number of new cancer cases in 2020 in Bangladesh, both sexes, all ages

In the current scenario, prostate cancer is exhibiting a heightened prevalence and mortality, registering 2,441 new cases accompanied by 1,289 fatalities in 2020. The cumulative prevalence over five years has reached 4,578, equivalent to a rate of 5.50 per 100,000 individuals [3].

Cancer is characterized by the uncontrolled growth and proliferation of cells, leading to the formation of malignant tumors [4]. The impact of cancer is undeniable, with millions of lives affected by its diagnosis, treatment, and often devastating consequences. To effectively combat this formidable adversary, a deep understanding of its genetic basis is of paramount importance.

The genetic basis of cancer is an intricate landscape of mutations, alterations, and dysregulations within the human genome. These genetic aberrations drive the initiation and progression of cancer, making them essential focal points for research and clinical practice. As Hanahan and Weinberg, (2011) [2] pointed out in their seminal work on the hallmarks of cancer, acquired genetic mutations underpin the hallmarks that define the cancer phenotype, including sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [2].

2. Methods

The evidence acquisition for this review involved a comprehensive search and analysis of relevant research articles, employing rigorous criteria for inclusion. The study authors systematically reviewed literature databases, including but not limited to PubMed, Research Gate, Google scholar, PMC free article to identify studies that addressed the genetic and epigenetic factors influencing cancer development, progression, and treatment. The selected articles were critically evaluated for their methodological robustness and relevance to the review's objectives. The evidence acquisition process prioritized recent publications while also considering seminal works to ensure a thorough understanding of the current state of knowledge in cancer genetics and epigenetics. This meticulous approach aimed to provide readers with a well-founded synthesis of existing findings and emerging trends in the field.

3. Results and discussions

3.1 Genetic Insights into Cancer

By uncovering the genetic alterations responsible for the development and progression of cancer, researchers and clinicians gain invaluable insights. This knowledge has direct implications in several critical areas:

3.1.1 Precision Medicine

The understanding of the genetic basis of cancer has ushered in the era of precision medicine. Personalized treatment strategies, tailored to the specific genetic profile of each patient's tumor, have emerged as a promising approach. Targeted therapies, such as imatinib for chronic myeloid leukemia or trastuzumab for HER2-positive breast cancer, have revolutionized cancer treatment, improving response rates and reducing side effects [5, 6].

3.1.2 Early Detection and Diagnosis

Genetic markers can serve as early indicators of cancer risk. Screening for inherited genetic mutations, such as BRCA1 and BRCA2 in breast and ovarian cancer, allows individuals at high risk to take preventive measures or undergo more frequent screening [7]. Moreover, liquid biopsies that detect circulating tumor DNA offer a minimally invasive method for diagnosing cancer and monitoring treatment response [8].

3.1.3 Development of Novel Therapies

As our understanding of cancer genetics deepens, new therapeutic targets continue to emerge. Immunotherapies, such as immune checkpoint inhibitors, have shown remarkable success in treating various cancer types. These treatments capitalize on the genetic factors that govern the interaction between cancer cells and the immune system [9].

3.2 Insights into Cancer Etiology

Investigating the genetic basis of cancer is shedding light on the complex interplay between genetics and environmental factors. This understanding is vital for developing preventive strategies, especially in cases where environmental exposures interact with genetic susceptibility [10]. In light of these crucial implications, a comprehensive review of the current state of knowledge regarding the genetic basis of cancer is essential. This review seeks to synthesize recent findings, highlight emerging trends, and provide a valuable resource for researchers, clinicians, and students interested in cancer genetics. Through a thorough search of research articles, we aim to explore the genetic mutations and epigenetic modifications associated with specific cancer types, discuss gene-environment interactions in cancer susceptibility, and consider the potential therapeutic targets and emerging treatment strategies based on genetic discoveries.

3.2.1 Epigenetic Regulation in Cancer: Role in Development and Progression

Cancer is not solely a product of genetic mutations; epigenetic regulation, the dynamic and reversible control of gene expression, also plays a pivotal role in cancer development and progression [11] This section delves into the significance of epigenetic changes in cancer, supported by a comprehensive search of research articles, and discusses how alterations in DNA methylation, histone modifications, and non-coding RNAs contribute to the disease.

Epigenetic Changes in DNA Methylation: One of the most well-documented epigenetic alterations in cancer is aberrant DNA methylation. DNA hypermethylation of promoter regions in tumor suppressor genes can result in gene

silencing, promoting uncontrolled cell growth. Conversely, DNA hypomethylation in gene body regions can lead to oncogene activation. For example, in colorectal cancer, hypermethylation of the MLH1 gene promoter results in microsatellite instability and contributes to carcinogenesis [12]. In addition, promoter hypermethylation of genes such as CDKN2A (p16) and RASSF1A has been observed in various cancer types, including lung and breast cancer, leading to cell cycle dysregulation and increased proliferation [13].

3.2.2 Histone Modifications in Cancer

Epigenetic regulation extends to histone modifications, such as acetylation, methylation, and phosphorylation, which can influence gene expression. Dysregulation of histone modifications contributes to cancer progression by promoting oncogene activation and inhibiting tumor suppressor gene expression. For instance, in breast cancer, histone deacetylation of the BRCA1 promoter is associated with decreased expression of this tumor suppressor gene, impairing DNA repair mechanisms [14]. In leukemia, fusion proteins like PML-RARα can lead to histone deacetylation, repressing genes essential for normal hematopoiesis [15]. Understanding the impact of histone modifications provides insights into novel therapeutic strategies targeting epigenetic regulators.

3.2.3 Non-Coding RNAs and Cancer Progression

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play a significant role in cancer by regulating gene expression at the post-transcriptional level. Dysregulated miRNAs can act as either tumor suppressors or oncogenes, depending on their target genes. In prostate cancer, miR-21 is overexpressed and promotes cell proliferation and migration by targeting tumor suppressor genes [16]. Conversely, miR-34a is downregulated in various cancer types and acts as a tumor suppressor by inhibiting genes involved in cell cycle progression and apoptosis [17]. LncRNAs also have critical roles in cancer progression; for instance, the HOTAIR lncRNA has been associated with increased metastasis and poor prognosis in breast cancer [18].

3.2.4 Therapeutic Implications and Future Directions

Understanding the epigenetic changes in cancer is of great clinical relevance. Epigenetic therapies, such as DNA demethylating agents (e.g., 5-azacytidine) and histone deacetylase inhibitors (e.g., vorinostat), have been developed and are used in the treatment of certain cancers. However, further research is needed to optimize these therapies and identify potential biomarkers for patient stratification. Additionally, exploring the crosstalk between genetic mutations and epigenetic alterations in cancer is an emerging area of research that promises to uncover new therapeutic targets [19]. Epigenetic regulation is a fundamental component of cancer development and progression. The interplay between genetic mutations and epigenetic changes is intricate and often drives oncogenesis. A comprehensive understanding of epigenetic mechanisms is crucial for the development of targeted therapies, diagnostic markers, and personalized treatment strategies in the fight against cancer.

3.3 Prostate Cancer: Genetic Associations, Signaling Pathways, and Variations

Prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer-related deaths among men in the United States [20]. This section provides an in-depth overview of the genetic associations, signaling pathways, and genetic variations associated with prostate cancer, supported by a thorough search of research articles.

3.3.1 Androgen Receptor (AR)

The androgen receptor gene (AR) is a key genetic player in prostate cancer. AR encodes a transcription factor that mediates the effects of androgens, such as testosterone and dihydrotestosterone. Genetic variations in AR, including polymorphisms and mutations, are associated with prostate cancer risk and progression. Amplification or overexpression of AR can lead to androgen hypersensitivity, contributing to the development and progression of prostate cancer [21].

The prostate, an androgen-regulated organ crucial for development and maintenance, has been extensively studied regarding androgens' role in carcinogenesis. Androgens, facilitated by the androgen receptor (AR), mediate the growth of the prostate, and the correlation between androgen levels and prostate cancer is well-established [22]. While androgen ablation therapy remains a primary treatment for metastatic prostate cancer, resistance often emerges due to genetic alterations, specifically somatic mutations in AR's hormone binding domain [23]. Genomic amplification of the AR gene further contributes to aberrant activation of the androgen-signaling axis, leading to treatment resistance [24]. Notably, somatic mutations are more prevalent in hormone refractory cases and metastases, emphasizing their role in altered androgen responsiveness [25].

On the other hand, AR amplification is linked to the failure of androgen deprivation therapy, particularly in tumors initially responsive to therapy [26]. The AR gene's microsatellite alterations, specifically shorter CAG repeats, are associated with an elevated risk of prostate cancer and aggressive tumor features. This comprehensive understanding of genetic variations in AR sheds light on the intricate mechanisms underlying prostate cancer development, progression, and therapeutic resistance.

3.3.2 BRCA1 and BRCA2

Mutations in the BRCA1 and BRCA2 genes, well-known for their associations with breast and ovarian cancers, also increase the risk of prostate cancer. Men with BRCA1 or BRCA2 mutations have a higher lifetime risk of developing aggressive forms of prostate cancer. These mutations play a role in DNA repair, and their dysfunction can lead to genomic instability in prostate cells [27].

3.3.3 HOXB13

The HOXB13 gene, a homeobox gene involved in embryonic development, has been linked to a significantly increased risk of hereditary prostate cancer. Rare germline mutations in HOXB13 are associated with a 20-fold increased risk of prostate cancer. The specific mechanisms by which HOXB13 contributes to prostate cancer are still being elucidated, but it appears to influence cellular proliferation and differentiation [28].

3.3.4 Androgen Signaling

Androgen receptor signaling is a fundamental pathway in prostate cancer. In the normal prostate, androgens promote cell growth and differentiation. In prostate cancer, aberrant androgen receptor signaling can occur through several mechanisms, including AR gene amplification, mutations, and ligand-independent activation. Targeting this pathway with androgen deprivation therapy remains a cornerstone of prostate cancer treatment [29].

3.3.5 PI3K/AKT/mTOR Pathway
The PI3K/AKT/mTOR pathway is frequently dysregulated in prostate cancer. Mutations and amplifications in key signaling components, such as PTEN, PIK3CA, and AKT, lead to increased cell proliferation, survival, and resistance to therapy. Targeted therapies that inhibit this pathway are being explored as potential treatment options [30].

3.3.6 Single Nucleotide Polymorphisms (SNPs)
Genome-wide association studies (GWAS) have identified numerous single nucleotide polymorphisms associated with prostate cancer risk. For example, SNPs in genes like RNASEL, MSMB, and KLK3 are associated with disease susceptibility. Some of these SNPs may modulate gene expression or protein function, contributing to prostate cancer development [31].

3.3.7 Copy Number Variations (CNVs)
Copy number variations, which involve the duplication or deletion of genomic segments, have been linked to prostate cancer. CNVs can affect oncogenes or tumor suppressor genes, influencing cancer susceptibility and progression [32].

3.3.8 Fusion Genes
Gene fusions, such as TMPRSS2-ERG, are common genetic events in prostate cancer. These rearrangements result in the overexpression of oncogenes, facilitating cellular transformation and promoting cancer development. TMPRSS2-ERG is one of the most prevalent fusion genes and is associated with aggressive prostate cancer [33].

Prostate cancer is a complex disease with a multifactorial etiology, involving both genetic and environmental factors. Understanding the genetic associations, signaling pathways, and variations that contribute to prostate cancer is critical for improved risk assessment, early detection, and the development of targeted therapies. Ongoing research continues to unravel the intricacies of prostate cancer genetics, offering promise for more effective and personalized approaches to managing this prevalent malignancy.

3.4 Structure of the Androgen Receptor (AR)
The androgen receptor (AR) is a protein that belongs to the nuclear receptor superfamily and plays a crucial role in mediating the effects of androgens, which include testosterone and dihydrotestosterone (DHT). AR is a transcription factor that regulates the expression of genes involved in various biological processes, including male sexual development, muscle growth, and prostate function. Its molecular structure is essential for its function in binding androgen ligands, interacting with co-factors, and initiating gene transcription. Here's an overview of AR's molecular structure:

3.4.1 N-Terminal Domain (NTD)
The N-terminal domain of AR contains a region rich in polyglutamine (polyQ) repeats and a transcriptional activation function (AF-1). This domain is responsible for AR's transcriptional activation.

3.4.2 DNA-Binding Domain (DBD)
The DBD contains two zinc fingers that facilitate DNA binding. This domain recognizes and binds to specific DNA sequences known as androgen response elements (AREs).

3.4.3 Hinge Region
This region connects the DBD and LBD and contains a nuclear localization signal (NLS) important for shuttling AR into the cell nucleus.

3.4.4 Ligand-Binding Domain (LBD)
The LBD is where androgen ligands, such as testosterone and DHT, bind to AR. It also contains the transcriptional activation function AF-2. Upon ligand binding, the LBD undergoes conformational changes necessary for AR activation [34]. Testosterone and DHT are lipophilic hormones that can diffuse through the cell membrane. In the absence of ligand binding, AR is located in the cytoplasm in an inactive state, bound to heat shock proteins (HSPs). Ligand binding triggers a series of conformational changes, including the release of HSPs and nuclear translocation of AR [35].

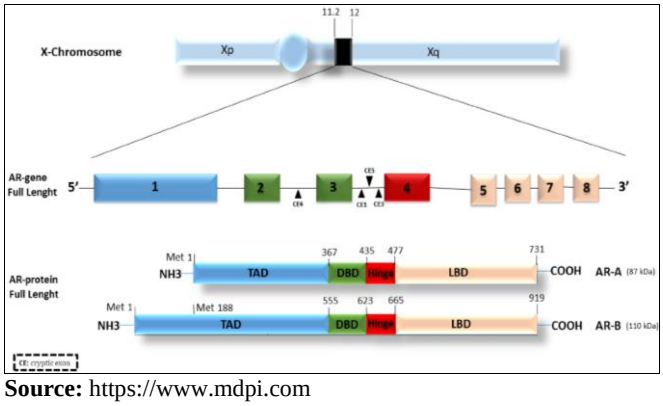
3.4.5 Nuclear Translocation
The hinge region of AR contains a nuclear localization signal (NLS) that facilitates its movement into the cell nucleus upon ligand binding.

3.4.6 DNA Binding and Transcription
The DBD of AR recognizes specific DNA sequences called androgen response elements (AREs) located in the promoters of target genes. Upon DNA binding, AR interacts with co-activators and co-repressors, leading to the initiation or suppression of gene transcription. The LBD contains the transcriptional activation function AF-2, which plays a crucial role in the transcriptional activation of AR target genes [36].

3.4.7 Post-Translational Modifications
AR undergoes various post-translational modifications, including phosphorylation, acetylation, and ubiquitination, which regulate its activity and stability.

3.4.8 Ligand-Induced Conformational Changes
The binding of androgens to AR induces a change in its conformation, allowing it to recruit co-activators and initiate gene transcription [37].

Understanding the molecular structure and function of AR is critical for the development of therapies targeting AR in conditions such as prostate cancer. Additionally, AR mutations and alterations can have significant implications for disease progression and treatment resistance, making them important areas of study in the field of prostate cancer research [38].



Source: https://www.mdpi.com

Fig 2: Androgen receptor structure and isoforms. The AR gene is located on the X chromosome and consists of 8 different exons encoding for three distinct functional regions: the TAD (transactivation domain), the DBD (DNA binding domain), and the LBD (ligand binding domain). The DBD and the LBD are linked by a hinge region. Different cryptic exons (CE) are located between exons, i.e., between exons 2, 3, and 4.

3.5 Normal Function of Androgen Receptor (AR)

The androgen receptor (AR) plays a crucial role in the normal development and function of the prostate gland. AR is a transcription factor that belongs to the steroid hormone receptor family. Its primary role is to mediate the biological effects of androgens, specifically testosterone and dihydrotestosterone (DHT). In the normal prostate, AR signaling is tightly regulated and essential for maintaining prostate homeostasis. Genetic variations in the androgen receptor (AR) gene play a significant role in the progression of prostate cancer. These variations can lead to altered AR function and androgen signaling, ultimately contributing to the development of advanced disease.

3.5.1 Prostate Development

During embryogenesis, AR signaling is pivotal for the development of the male urogenital tract, including the prostate gland. Activation of AR by androgens in target tissues induces the expression of specific genes that guide the growth and differentiation of the prostate [39].

3.5.2 Regulation of Prostate Growth

In the adult prostate, AR signaling continues to regulate the growth and maintenance of the gland. Androgens bind to AR, leading to the transcription of genes involved in cell survival, proliferation, and differentiation. This balanced regulation is essential for maintaining a healthy prostate [39].

3.5.3 Prostate Secretory Function

AR also plays a role in the secretory function of the prostate. It regulates the production of prostate-specific antigens (PSA) and other proteins, which are important for the liquefaction of semen and sperm motility [39].

3.6 Genetic Variations in AR and Prostate Cancer Progression

Genetic variations in AR are critical factors in the progression of prostate cancer. Alterations in the AR gene can lead to dysregulated androgen signaling, promoting the development of prostate cancer. Here, we discuss specific genetic variations and their consequences:

3.6.1 AR Amplification and Overexpression

Amplification of the AR gene and overexpression of AR protein are commonly observed in advanced prostate cancer. This results in an increased sensitivity of cancer cells to androgens. These amplified AR copies can drive the expression of pro-proliferative and anti-apoptotic genes, leading to tumor growth and resistance to therapy [14, 40]. This leads to a heightened sensitivity of cancer cells to androgens, even at low concentrations. Consequently, cancer cells become highly responsive to androgen signaling, driving cell proliferation and survival.

3.6.2 AR Mutations

Point mutations in the AR gene can confer altered ligand specificity, allowing AR to be activated by non-canonical ligands or even in a ligand-independent manner. Certain mutations, such as T877A, can lead to the activation of AR by progesterone or other steroid hormones. These mutations result in persistent AR signaling, even in the absence of physiological androgens, driving tumor progression [41]. This ligand-independent activation of AR can drive tumor progression and resistance to treatment, as observed in castration-resistant prostate cancer (CRPC) [42].

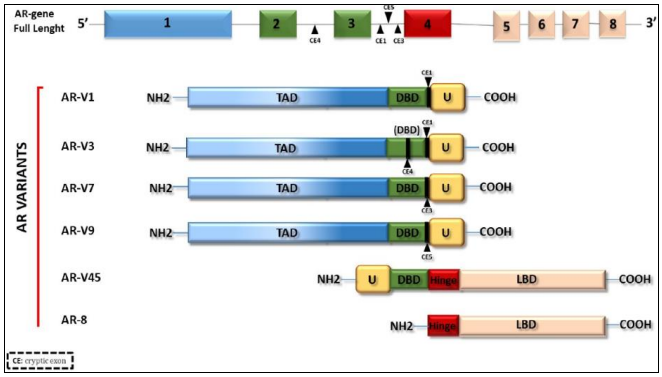
3.6.3 Splice Variants

Splice variants of AR, such as AR-V7, lack the ligand-binding domain (LBD) and are constitutively active. These variants are associated with resistance to androgen deprivation therapy (ADT). In patients with AR-V7-positive tumors, ADT becomes less effective, and these patients often progress to castration-resistant prostate cancer (CRPC) [43].

3.6.4 Glucocorticoid Receptor Cross-Activation

In some prostate cancer cases, genetic alterations in AR lead to a promiscuous receptor that can be activated by glucocorticoids, such as cortisol. This cross-activation sustains AR signaling even under conditions of low androgens and contributes to the progression of CRPC [44].

Understanding these genetic variations in AR is critical for the development of targeted therapies for advanced prostate cancer. Research into AR-targeted therapies, such as enzalutamide and abiraterone, has shown promise in suppressing aberrant AR signaling and improving outcomes in patients with advanced disease. Nevertheless, the continued exploration of AR genetic variations and their functional consequences is essential for refining treatment strategies and personalized medicine approaches for prostate cancer.



Source: https://www.mdpi.com

Fig 3: AR variants. The figure illustrates some of the naturally occurring AR variants. Most of them originate from AR alternative splicing

3.6.5 AR LBD Mutations

Mutations in the ligand-binding domain (LBD) of AR are common in prostate cancer. LBD mutations can result in altered AR function, leading to enhanced activation by androgens or even non-androgen ligands. For instance, the F877L mutation in the LBD causes resistance to anti-androgen therapy, as it promotes androgen receptor reactivation in the presence of anti-androgen drugs, leading to disease progression [45].

3.6.6 AR Ligand-Binding Pocket Mutations

Mutations in the ligand-binding pocket of AR can affect the binding affinity for androgens. These mutations can result in enhanced ligand binding or decreased ligand binding, ultimately impacting the responsiveness of AR to androgens. Such variations can lead to changes in the sensitivity of prostate cancer cells to androgen signaling, which can influence disease progression and response to androgen deprivation therapy [46].

3.6.7 AR Mutations in Treatment Resistance

Mutations in AR often arise as a mechanism of resistance to anti-androgen therapies. Resistance mutations can lead to a resurgence of AR signaling, despite treatment with anti-androgen drugs such as enzalutamide and abiraterone. These mutations may include amino acid substitutions in the AR gene, which enable the receptor to bind to anti-androgens more weakly or not at all. This allows AR to remain active,

promoting continued prostate cancer cell growth and survival [47].

Understanding the diversity of AR mutations is essential for tailoring treatment approaches in prostate cancer. Targeted therapies that address specific AR mutations or variants are actively being developed and investigated. Continued research in this area will improve the management of advanced prostate cancer and potentially identify new therapeutic strategies to overcome resistance.

4. Conclusions

In conclusion, this comprehensive review underscores the transformative impact of unraveling genetic alterations in cancer, elucidating pathways for precision medicine, early detection strategies, and the development of innovative therapies. By bridging the gap between genetic insights and clinical applications, this synthesis serves as a valuable resource for advancing cancer research and enhancing healthcare practices, fostering a future where tailored interventions based on genetic profiles revolutionize the landscape of cancer care.

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