

Review

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Review

Scaffolds, Sponges, and Steroids: Unraveling the RNA–Kinase Cross-Talk in Advanced Prostate Cancer

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Abstract

Prostate cancer remains a leading cause of male cancer mortality, principally due to the inevitable transition from androgen-sensitive disease to lethal castration-resistant prostate cancer (CRPC). This review synthesizes the multifaceted molecular mechanisms driving this therapeutic failure, moving beyond a catalogue of signaling nodes to a structural and kinetic analysis of resistance networks. We dissect the reactivation of Androgen Receptor (AR) signaling through the lens of key kinase cascades, specifically the PI3K/AKT/mTOR and MAPK axes, and their regulation of the steroidogenic gatekeeper CYP17A1. Special emphasis is placed on the structural determinants of CYP17A1 activity, including the critical Asn202 gating mechanism and the "backdoor" pathway of dihydrotestosterone (DHT) biosynthesis that bypasses canonical testosterone intermediates. Furthermore, we integrate the "hydrophobic spine" hypothesis of kinase activation to explain the efficacy and failure of Type I and Type II kinase inhibitors. In parallel, we unravel the regulatory complexity of non-coding RNAs (ncRNAs), detailing how upregulated transcripts like LINC00675 and Lnc-ZNF30-3 function as dynamic scaffolds and competing endogenous RNAs (ceRNAs) to stabilize AR and promote epithelial-mesenchymal transition (EMT). By converging these insights with emerging therapeutic strategies, such as next-generation lipid nanoparticle (LNP)-mediated RNA interference utilizing hexagonal HII phase endosomal escape, we provide a comprehensive roadmap for dismantling the molecular fortresses of advanced prostate cancer.

Keywords: prostate cancer; steroids; MAPK; androgen receptor; ncRNA

1. Introduction (Overview)

Despite the initial efficacy of Androgen Deprivation Therapy (ADT), the transition to lethal castration-resistant prostate cancer (CRPC) remains a pervasive clinical reality, driven by complex molecular adaptations [1–3]. The disease is primarily driven by elevated androgen levels, a condition known as hyperandrogenism [4]. Men over 65 are at higher risk of developing prostate cancer [5]. Androgen biosynthesis involves multiple enzymes, particularly cytochrome P450 enzymes, which regulate different stages of metabolism. A critical step in generating key androgen precursors, such as dihydrotestosterone (DHT) and dehydroepiandrosterone (DHEA), occurs in the adrenal gland and gonads and is catalyzed by CYP17A1 and HSD3 β 1 [6]. CYP17A1 is a membrane-associated hemoprotein located in the endoplasmic reticulum [7]. Crystallographic data reveals that substrate binding is highly specific; physiological substrates such as pregnenolone and progesterone bind within the active site at an angle of approximately 60 degrees relative to the plane of the heme group [8]. This orientation is not trivial; it is the structural determinant that dictates the site of oxidation.

The enzyme's dual functionality, acting as both a 17α -hydroxylase and a $17,20$ -lyase, is governed by subtle variations in this substrate positioning [9]. CYP17A1 is a major regulator of androgen production, exhibiting two distinct activities: hydroxylase and lyase [10–12]. CYP17A1 is indispensable for catalyzing critical steps in both the canonical and the alternative 'backdoor' pathways of androgen biosynthesis, positioning it as a metabolic linchpin in the reprogramming of prostate tumors. Through its hydroxylase activity, CYP17A1 hydroxylates the 17-carbon (C17) position of pregnenolone and progesterone, producing 17α -hydroxypregnenolone and 17α -hydroxyprogesterone, respectively [13]. Its $17,20$ -lyase activity then facilitates the conversion of these intermediates into DHEA and androstenedione, key precursors in testosterone synthesis [1]. Furthermore, CYP17A1 plays a crucial role in intratumoral androgen biosynthesis in castration-resistant prostate cancer (CRPC), emphasizing its significance in the treatment of advanced prostate cancer [14]. In the canonical pathway, cholesterol proceeds through pregnenolone to progesterone to androstenedione to testosterone to DHT. The backdoor pathway represents a metabolic detour that allows for the synthesis of potent androgens without passing through testosterone intermediates. This pathway is initiated by the 5α -reduction of 17α -hydroxyprogesterone by SRD5A1, a step that commits the steroid to the backdoor route. Subsequently, the reductive 3α -hydroxysteroid dehydrogenases (AKR1C2 and AKR1C4) convert 5α -pregnan- 17α -ol- $3,20$ -dione into 17OH -allopregnanolone. It is this intermediate that serves as the substrate for the CYP17A1 lyase reaction, yielding androsterone, often dismissed as a weak androgen or waste product, becomes the primary precursor in this pathway [15,16]. In CRPC, the upregulation of AKR1C3 facilitates the conversion of androsterone directly to androstanediol and finally oxidized to Dihydrotestosterone (DHT) by oxidative 3α -HSDs (like AKR1C3), thereby bypassing the therapeutic blockade of canonical testosterone synthesis [9]. In CRPC, tumors often upregulate AKR1C3 and SRD5A1. This allows the tumor to synthesize the most potent androgen, DHT, without ever producing testosterone and without relying on the adrenal precursors targeted by standard therapies. This explains why patients with undetectable serum testosterone can still have high intratumoral DHT and progressing disease.

The distinction between hydroxylase and lyase activity is the holy grail of CYP17A1 inhibition [17,18]. The $17,20$ -lyase reaction, which is the gateway to androgen production (converting C21 steroids to C19 androgens), requires an additional interaction with cytochrome b5 (cyt b5) [7,12,19]. The selectivity of CYP17A1 for 17α -hydroxypregnenolone over 17α -hydroxyprogesterone in the lyase reaction is not merely a matter of binding affinity (K_d), but of catalytic efficiency (k_{cat}). The presence of cytochrome b5 acts as an allosteric effector that accelerates the lyase reaction by orders of magnitude. This protein-protein interaction induces a conformational change in CYP17A1, likely widening the substrate access channel or altering the redox potential of the heme to favor the lyase reaction. The structural basis for this is likely the alteration of the redox potential of the heme iron, making it a more potent oxidant capable of attacking the C17-C20 bond. However, the Asn202 residue creates a hydrogen bond network that rigidly holds the substrate. For the lyase reaction to proceed, the substrate must possess a degree of flexibility to align with the activated oxygen species. The backdoor substrates, such as 17OH -allopregnanolone, possess a 3α -hydroxyl group and a planar A/B ring fusion (trans) that fits optimally into the active site even in the absence of cyt b5 facilitation, explaining why the backdoor pathway remains active even when canonical regulation is disrupted. Current inhibitors like abiraterone bind to the heme iron via a pyridine nitrogen, mimicking the substrate but blocking catalysis. However, because abiraterone inhibits both hydroxylase and lyase activities competitively, it leads to a buildup of upstream mineralocorticoids (like deoxycorticosterone), causing hypertension and hypokalemia. Future drug design must target the interface between CYP17A1 and cyt b5, or exploit the subtle metastable binding sites used during the multistep ligand entry process, to achieve lyase-specific inhibition. This would cut off androgen supply without disrupting cortisol biosynthesis, obviating the need for prednisone co-administration.

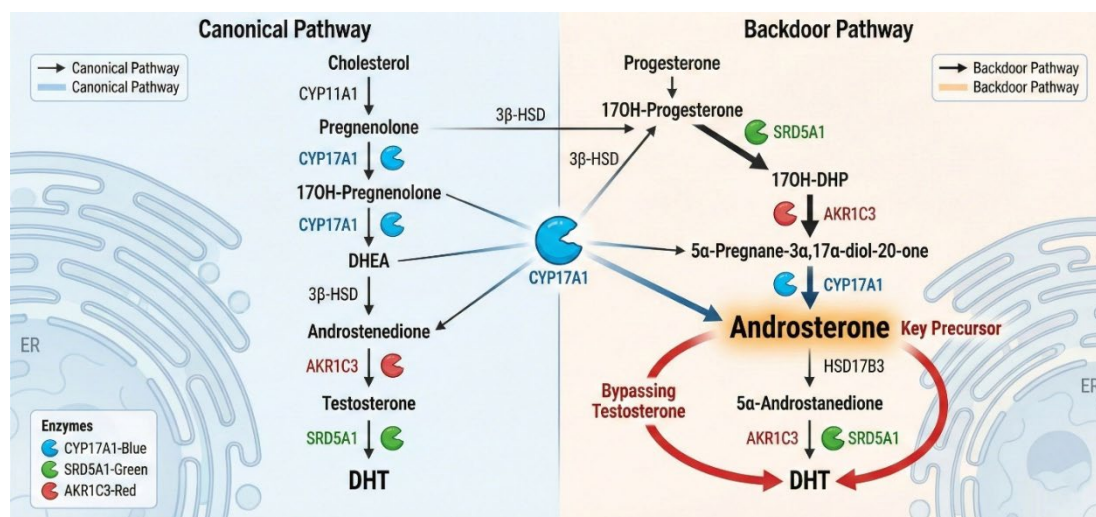


Figure 1. The "Backdoor" Pathway of Dihydrotestosterone (DHT) Biosynthesis. Metabolic flux diagram illustrating the alternative "backdoor" route prevalent in CRPC. Unlike the canonical pathway (left), which requires testosterone as an intermediate, the backdoor pathway (right) converts 17OH-Progesterone to DHT via 5 α -reduction (SRD5A1) and reductive 3 α -hydroxysteroid dehydrogenases (AKR1C2/4). The molecule androsterone serves as the key precursor in this pathway, ultimately oxidized by AKR1C3 to produce potent DHT without elevating serum testosterone levels.

Early-stage prostate cancer can be effectively treated with surgery or radiation therapy. However, once the cancer metastasizes, hormonal therapy, such as androgen deprivation therapy (ADT), becomes the primary treatment [20,21]. Despite the initial efficacy of ADT, the development of therapeutic resistance is a pervasive clinical reality. This resistance precipitates the transition to castration-resistant prostate cancer (CRPC), a lethal phenotype characterized by the reactivation of AR signaling despite castrate serum testosterone levels [22]. This resistance arises due to mechanisms such as androgen receptor (AR) mutations, abnormal activation, amplification, and alternative splicing of AR variants, which restore AR signaling and drive androgen-independent prostate cancer [2].

To address these challenges, research efforts have focused on developing alternative and combination treatments, leading to the targeting of androgen receptor pathways with therapeutic drugs like enzalutamide and apalutamide. Additionally, promising treatments such as PROTACs, PARP inhibitors, HDAC inhibitors, and immunotherapy are being explored [23,24]. Abiraterone, approved by the FDA in 2011, is used to treat prostate cancer by inhibiting CYP17A1 activity [25]. It is a selective inhibitor of both the lyase and hydroxylase activities of CYP17A1. The use of abiraterone has been shown to reduce prostate-specific antigen (PSA) levels, alleviate pain, and improve both survival rates and overall health in prostate cancer patients [26]. However, blocking CYP17A1 hydroxylase activity leads to excessive mineralocorticoid production, resulting in adverse effects such as hypertension, hypokalemia, and cardiovascular disorders [1,27,28].

Posttranslational phosphorylation of CYP17A1 at the serine/threonine domain by MAPK14 has been proposed to play a significant role in androgen biosynthesis by enhancing CYP17A1 17,20-lyase activity and promoting its interaction with cytochrome P450 oxidoreductase (POR) [29]. This molecular event is one of many downstream outcomes of the deregulated intracellular signaling cascades that underpin prostate cancer progression. Key oncogenic pathways include the PI3K/AKT/mTOR signaling axis, which is frequently activated due to loss of PTEN, a negative regulator of PI3K activity. PTEN loss, observed in a significant proportion of prostate cancer patients, leads to constitutive activation of AKT, promoting cell proliferation, metabolic adaptation, and resistance to apoptosis and ADT [30,31]. Simultaneously, AR signaling remains central to prostate tumor biology. Upon activation by androgens, AR translocates to the nucleus and regulates transcription of genes involved in growth, differentiation, and survival. Even under androgen-

deprived conditions such as after ADT prostate cancer cells often reactivate AR signaling through gene amplification, ligand-independent activation, or expression of constitutively active splice variants, sustaining tumor progression in the CRPC [32,33]. The EGFR/FGFR–MEK–ERK pathway also contributes significantly to disease progression, promoting cell cycle progression, proliferation, and survival via RAS-dependent and -independent mechanisms. The activation of this cascade supports mitogenic signaling and has been linked to therapeutic resistance[34].

Moreover, the TGF- β /SMAD signaling pathway exerts complex, stage-specific roles in prostate cancer. While it acts as a tumor suppressor in early stages by inducing cell cycle arrest and apoptosis, it paradoxically promotes epithelial–mesenchymal transition (EMT), immune escape, and metastasis during advanced disease. These dynamic signaling networks do not function in isolation; rather, they exhibit substantial crosstalk and feedback regulation, collectively driving tumor evolution, metastasis, and resistance to therapy [35,36].

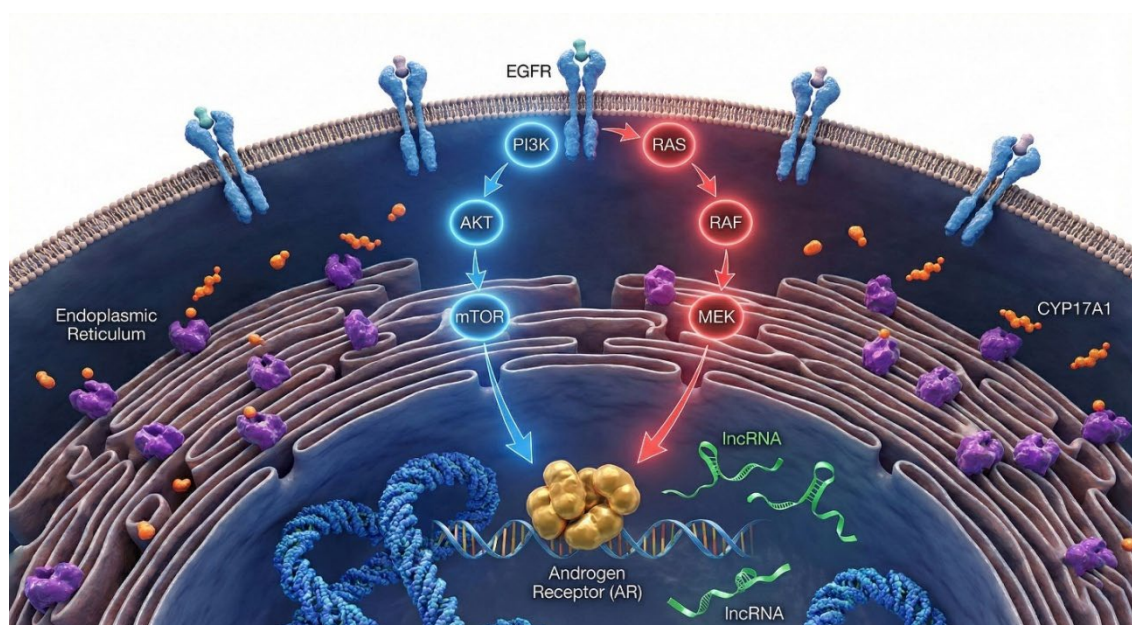


Figure 2. The Molecular Landscape of Castration-Resistant Prostate Cancer. A comprehensive visualization of the intracellular signaling networks driving CRPC. The diagram highlights the hyperactivation of the PI3K/AKT/mTOR cascade (blue) and its crosstalk with the Androgen Receptor (AR). The cytochrome P450 enzyme CYP17A1 enzymes (orange) on the Endoplasmic Reticulum, facilitates intratumoral steroidogenesis. In the nucleus, long non-coding RNAs (lncRNAs) act as scaffolds for chromatin-modifying complexes (PRC2), altering the epigenetic landscape to sustain survival gene expression.

Over the past decade, the field of RNA biology has been transformed by the discovery and functional characterization of non-coding RNAs (ncRNAs), including small interfering RNA (siRNA) and micro-RNA (miRNA), which are now recognized as regulators of gene expression. These gene expression control mechanisms occur at multiple levels, including post-transcriptional modification, mRNA processing, degradation, and translation. Based on protein-coding potential, RNA molecules are broadly categorized into coding and non-coding RNAs. Non-coding RNAs can be further categorized into regulatory RNAs which include short and long ncRNAs and housekeeping RNAs, including ribosomal RNA (rRNA) and transfer RNA (tRNA) [37]. In the context of prostate cancer, ncRNAs have gained increasing attention for their roles in tumorigenesis, progression, and therapeutic resistance. They modulate oncogenic and tumor suppressive pathways, including AR signaling, PI3K/AKT/MTOR, MAPK, P53, TGF- β 1 and mechanisms controlling mRNA stability. Furthermore, ncRNAs influence post-translational modifications, proteasome-mediated ubiquitination, and the degradation of AR and other regulatory proteins [38,39]. These multifaceted functions show their potential as both therapeutic targets and diagnostic biomarkers in advanced

prostate cancer. Therefore, this review aims to explore the interplay between kinase signaling pathways and ncRNA-mediated regulation in prostate cancer, with a focus on therapeutic implications and future opportunities for precision medicine.

2. Signaling Through Protein Phosphorylation

Signal transduction within the cell is driven by various stress stimulus and is tightly regulated to control essential cellular functions. These processes are important for cell survival under both normal and pathological conditions. Mediators of these signals can activate or deactivate signaling cascades, thereby regulating cellular mechanisms such as growth, replication, survival, and apoptosis to maintain cellular homeostasis [40]. Aberrant protein phosphorylation is a hallmark of CRPC, driving tumor plasticity and drug resistance. This signaling deregulation is not merely a downstream effect but a driver of the transition to androgen independence. Protein phosphorylation is a reversible post-translational modification that involves the transfer of a phosphate group to a specific amino acid residue on a substrate [41]. In contrast, dephosphorylation removes a phosphate group from the substrate, often transferring it to water molecules to deactivate its function. The dynamic interplay between phosphorylation and dephosphorylation acts as a molecular switch, modulating the structural and functional protein conformation, interactions with other molecules, and subcellular localization in response to intracellular and extracellular stimuli [40]. This regulatory circuit is essential for controlling numerous cellular events, including enzyme activity, cell division, aging, protein synthesis, metabolism, and signal transduction [42].

2.1. Protein Kinases

Protein kinases (PKs) constitute approximately 2% of the eukaryotic genome yet regulate the post-translational modification of over 30% of the cellular proteome [43,44]. The catalytic efficiency of protein kinases in prostate cancer oncogenesis is governed by the dynamic assembly of the 'Regulatory (R) Spine,' a non-contiguous vertical stack of four hydrophobic residues (RS1-RS4) that connects the N-terminal and C-terminal lobes. In the inactive state, this spine is disassembled; upon activation, often driven by upstream signaling or oncogenic mutation, the spine residues align to stabilize the active conformation, facilitating ATP binding and substrate phosphorylation. Understanding this 'spine switch' is critical for the design of next-generation kinase inhibitors in PCa. Type I inhibitors target the assembled spine (active conformation), often leading to adaptive resistance, whereas Type II inhibitors stabilize the disassembled spine (inactive conformation), potentially offering more durable suppression of oncogenic drivers like BRAF and AKT [45]. Protein kinases are broadly grouped into three major classes based on the amino acid domain they phosphorylate: serine, threonine and tyrosine. Additionally, dual specificity kinases have also been identified as kinases that can act as serine, threonine and tyrosine [45,46]. PKs contain a catalytic domain which comprises C- and N- subdomains that act together as an active site of the protein [47]. This catalytic domain is normally inactive due to inward rotation of C-and N- lobes but upon activation via phosphorylation induces rearrangements on the protein, allowing non-catalytic domain of the protein to interact and recruit the substrates and activate other signaling proteins or cascades [41].

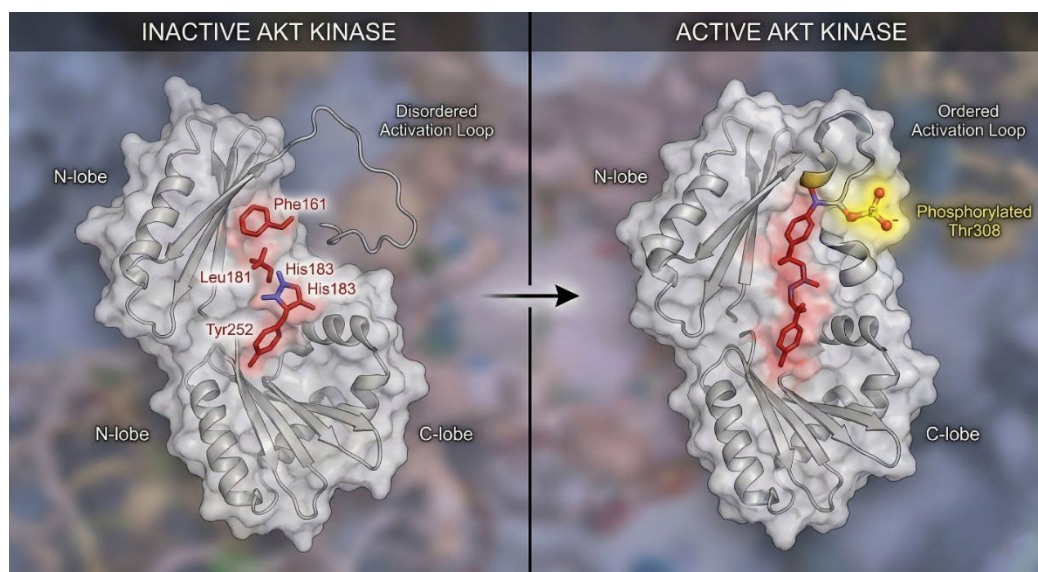


Figure 3. Structural Dynamics of Kinase Activation: The Hydrophobic Spine. Comparison of the inactive (left) and active (right) conformations of the AKT kinase domain. In the inactive state, the Regulatory (R) spine residues are misaligned, and the activation loop is disordered. Upon phosphorylation (yellow glow), the N-lobe and C-lobe close, forcing the R-spine residues into a continuous vertical stack. This "spine assembly" rigidifies the catalytic cleft, enabling ATP binding and substrate phosphorylation.

2.1.1. Serine/Threonine Kinases

Serine/threonine kinases which constitute the larger group of protein kinases, are known to phosphorylate through the hydrolysis of OH group and transferring of phosphate to the serine/threonine residues of the substrates. They can be activated in response to signals such as DNA damage or Ca^{2+} mediated chemical signaling [41]. The major classes of serine/threonine kinases include second messenger dependent kinases (cAMP, protein C, cGMP, and Ca^{2+} or calmodulin kinases), MAP kinases (ERKS, JNKs), MAP Kinase-regulating kinases (MEKs, SEKs, Raf, MEK kinases), CDKs (Cdc-2) CDK-regulating kinases (CAK, CAK kinase). Their activation is via N- and C-termini lobes, where N-terminal is responsible for binding and hydrolyzing ATP, while C-terminal binds to the substrate to transfer the phosphate group; thereby, activating the downstream cascades.

2.1.2. Tyrosine Kinases

Tyrosine kinases (TKs) catalyze the transfer of the γ -phosphate from ATP to the phenolic hydroxyl group of tyrosine residues. This modification frequently generates high-affinity docking sites for SH2 and PTB domain-containing proteins, thereby nucleating multiprotein signaling complexes at the plasma membrane [48,49]. TKs, which are regulated by posttranslational modification are classified into two major subfamilies: receptor tyrosine kinases (e.g. EGF, VEGF, PDGF) and non-receptor tyrosine kinases [50]. TKs contains ligand binding and transmembrane domains, which enables them to interact with ligands and other proteins through outer membrane to activate tyrosine domain that is critical in mediating their intracellular signaling pathways [51]-[53]. Furthermore, TKs are involved in the activation of many signaling cascades, hence mutations or any abnormalities in the regulation of these signals has been linked with several diseases including atherosclerosis, diabetes, inflammations, cancer and angiogenesis [54]. In the context of prostate cancer, non-receptor tyrosine kinases (NRTKs) such as Src and Etk play pivotal roles in androgen-independent growth. Src kinase, for instance, physically interacts with and phosphorylates the Androgen Receptor (AR) at Tyr534, a modification that sustains AR transcriptional activity even in

androgen-depleted environments. This Src-AR axis represents a major escape mechanism from ADT, rendering the receptor sensitive to low levels of adrenal androgens or even non-androgen ligands. [48,49]

2.2. Protein Phosphatases

Protein phosphatases (PPs) are hydrolases that antagonize protein kinases via hydrolysis of removing the phosphate from substrates to activate or regulate their specific activity. Just like PKs, PPs contain tyrosine and serine/threonine residues with approximately 107 of phosphates having tyrosine and 30 phosphatases with serine/threonine residues, respectively. Protein serine/threonine phosphatases can further be classified into three subfamilies: phosphoprotein phosphatases (PPPs) [such as protein phosphatases (PP1, PP2, PP4, PP5)], metal-dependent protein phosphatases (PPMs) (such as PP2C, which depend on magnesium Mg^{2+} / manganese Mn^{2+} ions) and aspartate-based phosphatases [55]. Due to their roles in helping to maintain the molecular switching between phosphorylated and unphosphorylated state, PPs have been postulated to regulate many important signals including the process of tumorigenesis. For instance, PTEN, which is negatively regulated by PI3K, can act as tumor suppressor as its downregulation has associated with tumorigenesis progression in many cancer types [56]. Similarly, the downregulation of PP2A and Src homolog region 2 domain-containing phosphatase-2 (SHP2) in tumorigenesis has been well documented. SHP2 are involved in the regulation of downstream signal of growth receptor like RAS [57], while PP2A acts a tumor suppressor via dephosphorylation of kinase-induced signaling leading to progression of cancer. Therefore, dysregulation of these phosphatases can promote tumorigenesis, making them a good druggable candidate against cancer [58,59].

2.3. In Vitro and In Vivo Assays Targeting Kinases in Human Diseases

The ability to measure kinases *in vitro* activity is important to assay for their capability to transfer γ -phosphate and phosphorylate substrates from the donor substrates to acceptor protein [60,61]. Several commercially available phosphor-specific antibodies are used to stimulate phosphorylation sites within a given kinase [62]. This is important to determine if the kinase used is responsible for catalyzing the phosphotransfer by using a standardized kinase assay [63].

The role of protein kinases in tumorigenesis has been well documented and their identification has helped to explain the evolution of many cancer types, which makes them an ideal target for cancer treatment. For instance, many classes of phosphoinositide kinases, most especially, PI3K have been targeted *in vivo* and *in vitro* for the treatment of human diseases including neurodegenerative, viral infections, and prostate and breast cancer [64]. This is due to their crucial roles in trafficking and signaling transduction across membranes. Similarly, tyrosine kinases including JAK, SYK, TEC families and Rho kinase, ABL kinase and NAK kinase has been targeted for treatment due to their modulating roles in signaling pathways involve in immunodeficiency diseases including autoimmune disorders, hematological malignancy, allergic disorders and covid-19 [65,66].

3. Non-Coding RNAs (ncRNAs)

RNA interference (RNAi) technology is a powerful molecular tool used to regulate post-transcriptional processes by silencing mRNA in a sequence-specific manner. Its therapeutic potential lies in its ability to precisely target and inhibit specific mRNA, leading to gene silencing. This approach has shown promise in treating various human diseases, including cancers, viral infections, and genetic disorders, particularly those involving peptide products that are traditionally considered undruggable [67,68].

3.1. Small Non-Coding RNA (sncRNAs)

sncRNAs are the heterogeneous group of untranslated transcripts, which include siRNA, miRNA and piwi-interacting (piRNA). This classification is based on their structures, origins, biological roles, and associated proteins [69]. Recently, many studies have been oriented towards sncRNAs because of their diverse roles in regulating gene expression. While the housekeeping sncRNA such as tRNA and rRNA are involved in the maintenance of ribosomal formations, the critical roles of regulatory sncRNA such as siRNA, miRNA and piRNA in modulating gene expression has been well documented [69,70].

3.1.1. Micro-RNA (miRNA)

miRNA encompass a single-strand and functional RNA that does not code for proteins but is produced to play critical roles in the regulation and repression of many biological processes at a genomic level. miRNA is the most studied class of sncRNA, and it has been demonstrated that a single miRNA can bind and regulate many mRNAs translation through its multiple target sites, which increases repression efficiency [71,72]. In prostate cancer, miRNAs act as tumor suppressors or oncogenes:

Tumor-suppressive miRNAs: miR-34a, let-7b, miR-141, miR-15a/miR-16-1 cluster, and miR-133a-3p inhibit PCa cell proliferation, invasion, and metastasis, often by inducing apoptosis, cell cycle arrest, or targeting pathways such as EGFR/AKT [73]-[75]. miR-195 and miR-203 similarly suppress invasion and EMT in PCa.

Oncogenic miRNAs: miR-452, miR-301b, miR-210-3p, miR-375, miR-21, miR-32, miR-106b, and miR-221/222 are upregulated in PCa, promoting EMT, bone metastasis, stemness, and therapy resistance via pathways including NF- κ B, Wnt/ β -catenin, and SEC23A [73,75]-[78].

Following the maturation and activation mediated by RNase III enzymes, miRNA either binds to 3' untranslated regions (3'UTRs) or/and the promoter regions of mRNA to mediate translation repression or mRNA degradation [79,80].

3.1.2. siRNA

siRNA is a non-coding, double stranded RNA oligonucleotide with roughly 20-24 base pairs (bp) in length and its production is catalyzed by a dicer enzyme, which catalyzes the cleavage of poly A tail. Upon activation, siRNA can specifically target and prevent the translation of many mRNA transcripts [81]. Since the first discovery in plants and later in roundworm (*c. elegans*) and subsequently in mammalian cells, siRNA has attracted serious interest because of its ability to specifically target and inhibit a particular gene in several human diseases including cancer. This makes it an ideal therapeutic target in the treatment of these diseases. The phenomenon of using dsRNA to silence or inhibit post-transcription of genes or to mediate mRNA degradation is called RNA interfering (RNAi) technology.

3.1.3. piRNAs

piRNAs are small RNAs that associate with Piwi proteins to regulate gene expression epigenetically. In PCa, PIWIL2 is upregulated and enhances EMT, invasion, and metastasis, contributing to tumor progression [82].

3.2. Long Non-Coding RNAs (lncRNAs)

lncRNAs includes enhancer RNAs (eRNAs), circular (ciRNAs), intergenic RNAs and natural antisense transcripts (NATs) have attracted a wide range of research interest due their roles in chromatin remodeling, RNA splicing, transcription, and translation [83]. In addition, lncRNAs has been implicated in VDJ recombination and class switching of immune cells, p53 mediated DNA damage responses, regulation of cholesterol metabolism as well as developmental stage in animals, making them an ideal target in human diseases [84].

In PCa, lncRNAs can be oncogenic or tumor-suppressive. Oncogenic lncRNAs: HOTAIR, Lnc-ZNF30-3, CRNDE, MALAT1, TERC, PCAT1, PCAT6, DANCR, and LINC00675 are upregulated, promoting proliferation, invasion, metastasis, and therapy resistance via chromatin modification, Wnt/ β -catenin, PI3K/AKT, and NF- κ B pathways [82,85,92].

Tumor-suppressive lncRNAs: PCAT29, DRAIC, GAS5, and MEG3 are downregulated and inhibit migration, metastasis, and NF- κ B signaling, acting as negative regulators of PCa progression [86]. LINC00675 has a dual role, where its downregulation contributes to castration-resistant PCa and therapy resistance [89].

Due to their various functions in many important physiological events, alteration in their gene expression pattern has implications in the development of many diseases making them an ideal biological marker, which holds therapeutic strategies [93]. The roles of lncRNA in prostate cancer and progression to CRPC have been documented, and it is mediated through several mechanisms including chromatin remodeling, recruitment of chromatin modifiers and post-transcriptional regulation via interaction with proteins or RNAs.

Long non-coding RNAs (lncRNAs) like HOTAIR do not merely float in the nucleus; they act as flexible scaffolds. HOTAIR possesses specific secondary structures (hairpins) that serve as docking sites for protein complexes. The 5' domain of HOTAIR binds to EZH2, the catalytic methyltransferase subunit of the Polycomb Repressive Complex 2 (PRC2). Simultaneously, the 3' domain can bind to the LSD1/CoREST/REST complex (a demethylase). By bridging these two complexes, HOTAIR coordinates a double hit on chromatin: it guides PRC2 to deposit repressive H3K27me3 marks (trimethylation of lysine 27 on histone H3) while LSD1 removes active H3K4me2 marks. This creates a massive block of heterochromatin, silencing tumor suppressor genes. Recent data suggests this is not just random recruitment; RNA matchmaking occurs where HOTAIR interacts with the target gene's nascent RNA transcripts via base-pairing, stabilizing the PRC2 complex at that specific locus. This RNA-RNA interaction relieves the autoinhibition of PRC2, activating its methyltransferase activity specifically at the target site. This insight suggests that blocking the RNA-RNA interaction surface could be a more specific therapy than global EZH2 inhibitors. A variety of non-coding RNAs, including microRNAs, long non-coding RNAs, piRNAs, and circular RNAs, have been implicated in prostate cancer, with 9 upregulated and 6 downregulated molecules identified (Table 1).

Table 1. Differential Expression and Functional Roles of Non-Coding RNAs in Prostate Cancer Progression.

RNA Type	Name	Classification	Expression in PCa	Functional Roles	Reference(s)
miRNA	miR-34a, let-7b, miR-141, miR-106	Tumor-suppressive microRNAs	Downregulated	Inhibit prostate cancer (PCa) cell invasion by inducing apoptosis and arresting the cell cycle	[74]
miRNA	miR-452, miR-301b	Oncogenic microRNAs	Upregulated	Enhance invasion and stemness of cancer stem cells (CSCs)	[76,78]
miRNA	miR-15a/miR-16-1 cluster	Tumor-suppressive microRNAs	Downregulated	Induce apoptosis and cell cycle arrest in PCa cells via targeting BCL2	[73]
miRNA	miR-133a-3p	Tumor-suppressive microRNA	Downregulated	Inhibits viability and invasion of PCa cells by promoting apoptosis; may regulate EGFR/AKT pathway	[75]
miRNA	miR-210-3p	Hypoxia-induced oncogenic microRNA	Upregulated	Drives epithelial-mesenchymal transition (EMT)	[94]

				and bone metastasis via NF-κB pathway activation	
miRNA	miR-375	Oncogenic microRNA	Upregulated	Facilitates PCa progression, possibly via targeting SEC23A	[77]
lncRNA	HOTAIR	Oncogenic lncRNA	Upregulated	Enhances PCa cell proliferation and invasion; modulates chromatin state via PRC2 complex	[92]
piRNA	PIWIL2	Oncogenic piRNA-associated protein	Upregulated	Promotes EMT, invasion, and metastasis; potential role in epigenetic silencing	[82]
lncRNA	Lnc-ZNF30-3	Oncogenic lncRNA	Upregulated	Enhances PCa cell survival and correlates with poor prognosis in patients. acting as a competitive endogenous RNA (ceRNA) sponge for miR-145-5p, thereby derepressing the EMT driver TWIST1	[91]
lncRNA	CRNDE	Oncogenic lncRNA	Upregulated	Stimulates PCa cell proliferation, migration, and invasion through Wnt/β-catenin signaling	[90]
circRNA	circ-0005276	Oncogenic circular RNA	Upregulated	Promotes proliferation and invasion of PCa cells, likely via miRNA sponging	[87]
lncRNA	MALAT1	Oncogenic lncRNA	Upregulated	Inhibits apoptosis and promotes PCa invasion by regulating EMT-related genes	[88]
lncRNA	PCAT29, DRAIC	Tumor-suppressive lncRNAs	Downregulated	Inhibit migration and metastasis of PCa cells; DRAIC interacts with IKK complex to suppress NF-κB	[86]
lncRNA	LINC00675	Dual function lncRNA in CRPC	Upregulated	Promotes castration-resistant prostate cancer (CRPC) progression and therapy resistance. Direct binding to the AR N-terminal domain, which blocks MDM2 interaction, preventing ubiquitination and degradation	[89]
lncRNA	TERC (Telomerase RNA Component)	Oncogenic lncRNA	Upregulated	Supports tumor progression by maintaining telomere	[85]

3.3. Mechanism of Action of RNAi Silencing

RNAi is a cellular natural phenomenon that mediates gene expression silencing using dsRNA to promote sequence specific mRNA degradation. Using the knowledge obtained from *c. elegans*, it was demonstrated that plants possess a specialized RNA-dependent RNA polymerase (RDRP) when triggered by high cellular level of messenger RNA. In response, RDRP creates dsRNA to shut down gene expression at posttranscriptional level in *petunia hybrida* plant [95,96]. Subsequently, a similar process was observed in mammalian cells [97]. In recent years, the knowledge and understanding of underlying mechanisms of RNAi technology has substantially grown and is well understood. It is now understood that ncdsRNA either biologically transcribed or artificially incorporated into the cells can be cleaved by the Dicer enzyme (called ribonuclease III) into short base pairs of about 21-25 nucleotide sequence called siRNA [98]. Upon activation, siRNA can interact and activate a multiprotein complex called RNA-induced silencing complex (RISC) or RISC loading complex [99]. RISC comprises endonuclease argonaute 2 (AGO2) and other RISC associated proteins such as TAR RNA binding protein (TRBP). AGO2 facilitates the thermodynamic unwinding and subsequent endonucleolytic cleavage of the passenger strand. AGO2 is the catalytic heart of RNAi. It possesses a bilobal architecture comprising four domains: N, PAZ, MID, and PIWI. The molecule is shaped roughly like a crescent or a duck. The MID domain contains a specific binding pocket that anchors the 5' phosphate of the miRNA or siRNA guide strand. This anchoring is critical; it sets the "register" for determining the seed sequence. The PAZ domain anchors the 3' end of the small RNA. Loading the RISC is a dynamic physical process. Structural studies reveal that when AGO2 binds a target mRNA that is complementary to the guide strand, the protein undergoes a dramatic conformational change. The PAZ domain releases the 3' end of the guide RNA, and the N-PAZ lobe rotates away from the MID-PIWI lobe. This "widening" of the central channel allows the guide RNA and target mRNA to propagate their double-helix pairing beyond the seed region without steric hindrance [100,101]. Thereafter, the antisense strand directs the RISC complex to its complementary target mRNA and effectively causes specific gene silencing at posttranscriptional level [99,102]. This structural flexibility is what makes RNAi potent but also vulnerable. In PCa cells, oncogenic environments (hypoxia, stress) can lead to post-translational modifications of AGO2 (e.g., phosphorylation by MAPK) that might impair this conformational flexibility. Furthermore, the slicer activity resides in the PIWI domain, which folds like RNase H. If the pairing is perfect (as with siRNA therapeutics), the PIWI domain positions the mRNA backbone exactly near catalytic aspartate residues for cleavage. If pairing is imperfect (as with most endogenous miRNAs), slicing does not occur, and translational repression follows. Therapeutic siRNAs must be designed to maximize this slicer conformation.

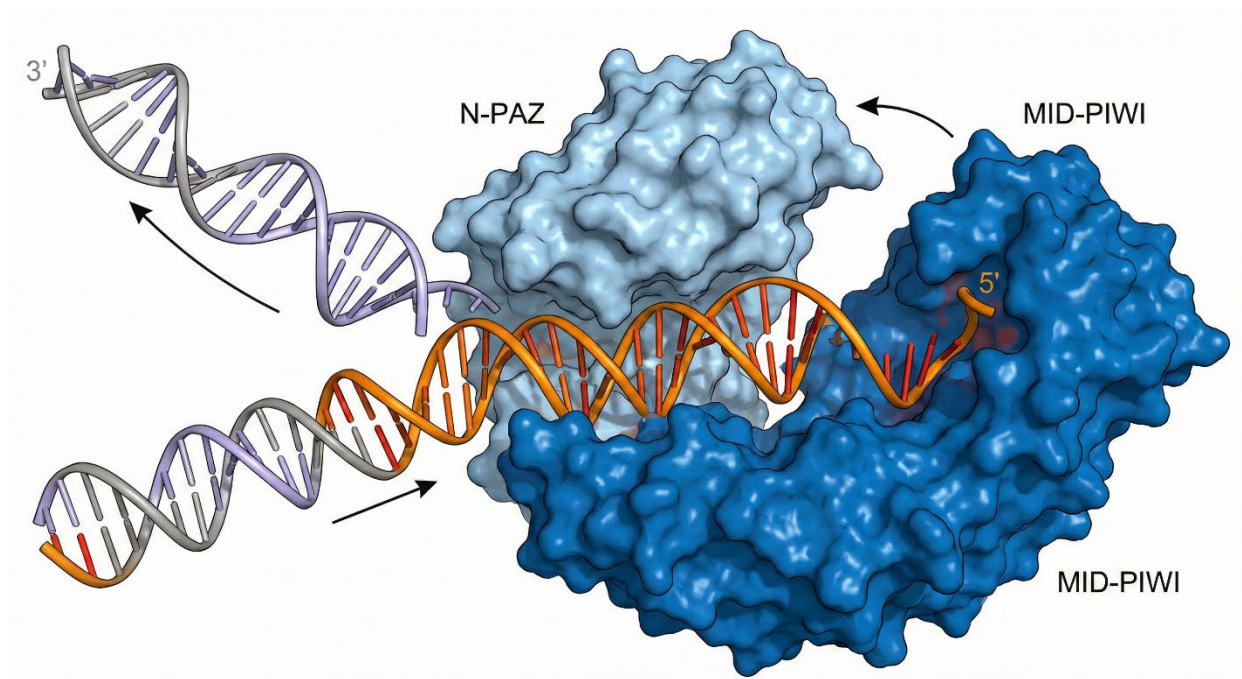


Figure 4. Conformational Dynamics of the RISC Loading Complex. Mechanism of Argonaute 2 (AGO2) loading. The AGO2 protein (blue) is shown in its bilobal open state. As the double-stranded small RNA enters the central cleft, the PAZ domain anchors the 3' end while the MID domain anchors the 5' phosphate. The protein undergoes a structural widening to separate the passenger strand (peeling away) from the guide strand (orange), which remains threaded in the channel to direct gene silencing.

3.4. Advantages and Disadvantages of RNAi Technology

RNAi technology remains a cornerstone and widely used technology in biochemical and biological research to effectively knockdown a target mRNA sequence. It offers several advantages over conventional methods of gene silencing vectors, which include highly specific suppression of gene expression and less off-target effects [103]. Despite the progress that have been made with application of RNAi technology to effectively inhibit a specific gene and combat human diseases, it has been faced with several challenges including off-target silencing, degradation of closely related that are not identical mRNA genes, inability to pass through cellular membrane due to net negative charge, less success rate of 1 in 3 ratios and delivery issues [104,105]. To overcome these barriers, Lipid Nanoparticles (LNPs) have been engineered to facilitate endosomal escape. When Lipid Nanoparticles (LNPs) carrying siRNA are endocytosed, they are trapped in endosomes. As the endosome matures and acidifies, the ionizable lipids in the LNP become protonated (positively charged). This allows them to interact electrostatically with the anionic lipids of the endosomal membrane. This interaction induces a phase transition in the lipids from a lamellar (bilayer) phase to a hexagonal HII phase. This non-bilayer structure is fusogenic, it disrupts the integrity of the endosomal membrane, creating transient "fusion pores" through which the RNA cargo can escape into the cytosol. [106]. However, research shows this escape efficiency is remarkably low (often <2%). Most LNPs are degraded in lysosomes or recycled/exocytosed. The next-generation LNPs are being engineered with specific lipids (like phytosterols or specific ionizable tails) that lower the energy barrier for this hexagonal phase transition, thereby enhancing cytosolic bioavailability.

3.5. Roles of Non-Coding RNA in Prostate Cancer

Over the years, the paradigm shifts towards targeting RNAi gene silencing has been propelled by the identification of non-coding RNA cancer-related genes for their oncogenic or tumor suppressor potential. The roles of ncRNA in different types of cancer have been highlighted. For instance, overexpression of long non-coding RNA (HOTAIR) and dysregulation of piwi-interacting (piRNA)

have been linked with breast cancer, while deregulation of microRNA (miR-15 and miR-16) has been associated with chronic lymphocytic leukemia [107]. Similarly, the identification of lncRNAs (PRCR1 and PCGEM1) binding to androgen to induce the transcription of over 200 AR-responsive genes correlates with the aggression and progression of the PCa [108]. In mouse model, deletion of miR-15a-miR-16-1 cluster resulted in PCa cells survival, proliferation, and invasion, whereas overexpression led to regression characterized by increased apoptosis and cell cycle arrest [107].

In bone metastasis PCa, upregulation of miRNAs (such as miR-133a-3p, miR-466, miR-210 and miR-375) were found to control the inhibition or promotion of the important signaling pathways including wnt signal, transforming growth factor β (TGF- β), AKT, nuclear transcription factor-kB (NF-kB), which are crucial for PCa progression, recurrence and response to therapy [109,110]. Importantly, the oncogenic miR-21 promotes tumorigenesis by targeting PTEN and driving persistent PI3K/AKT signaling, while the tumor suppressor miR-34a regulates MET and NOTCH1, thereby modulating apoptosis and epithelial-to-mesenchymal transition (EMT), further augmenting the context-specific role of ncRNAs in prostate cancer biology [111,112]. The increased expression of Lnc-ZNF30-3 in PCa was associated with poor prognosis, possibly via its interaction with AGO2 complex and miR145-5p and mediating gene silencing [91]. Through the regulation of miR-146a-5p and suppression of miR-101 mediated inhibition of Ras-related oncogenic protein 1A, lncRNA CRNDE can inhibit apoptosis while up-regulating the metalloproteases like MPP-2 and MPP-9, thereby promoting cell invasion and proliferation in PCa cells [113]. The knock-down of SNHG4 which regulate RRM2 expression led to significant increase in cell senescence and cell cycle arrest, whereas overexpression resulted PCa cells resistance to enzalutamide in *in vitro* and mouse model [114]. The roles of ncRNAs in PCa in bone metastasis cannot be overemphasized as overexpression of these RNAs has been reported, which correspond with either invasion or inhibition of PCa progression. PCa progression coupled with epithelial-to-mesenchymal transition and resistance to therapy has been attributed to circular non-coding RNA (hsa-circ-0005276/FUS axis) via the upregulation of XIAP [115]. In addition, circZNF609 promotes cell proliferation by sponging miR-186-5p and activating AKT signaling, adding another layer of circRNA-mediated oncogenic regulation [116].

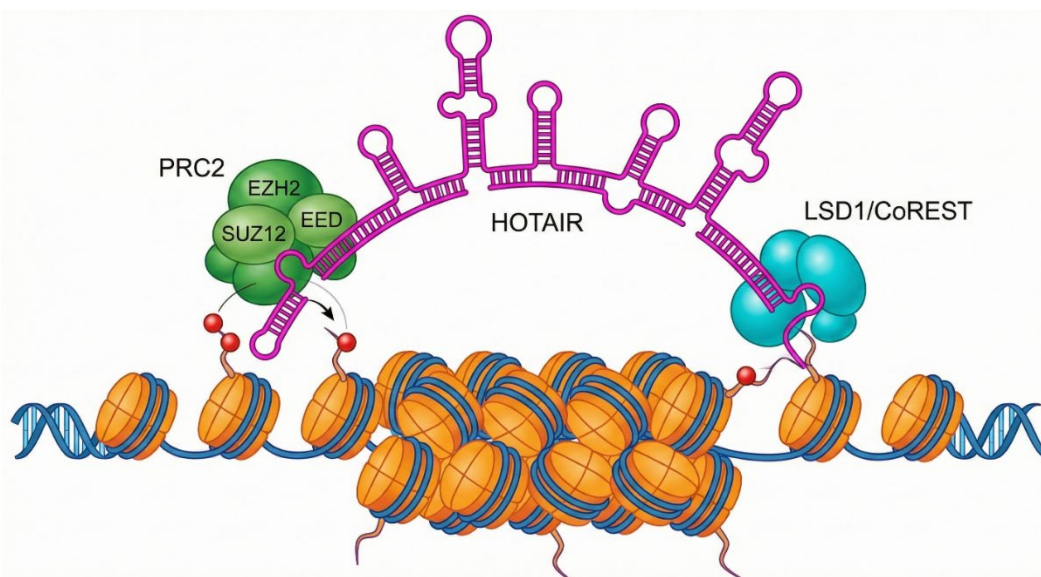


Figure 5. lncRNA HOTAIR as a Chromatin Scaffold. Schematic of the long non-coding RNA HOTAIR functioning as a molecular bridge. The 5' domain of HOTAIR recruits the Polycomb Repressive Complex 2 (PRC2), responsible for H3K27 trimethylation (repressive mark), while the 3' domain recruits the LSD1 demethylase complex. This simultaneous recruitment coordinates the formation of heterochromatin, silencing tumor suppressor genes in metastatic prostate cancer cells.

Overexpression of MALAT1 PCa was associated with metastasis and progression of castration-resistance prostate cancer, whereas its downregulation using siRNA has been reported to inhibit PCa invasion and progression marked with increased cell cycle arrest in G0/G1 phase in both *in vivo* and *in vitro* [117,118]. Nevertheless, the downregulation and low-level expression of lncRNAs (PCAT29 and DRAIC) has been associated with progression to CRPC in androgen-dependent manner in PCa patients at high risk of biochemical recurrence [86,117]. Similarly, overexpression of GAS5 in LnCaP, 22-RV-1 and PC-3 cells was associated with reduced cell viability, which sensitized cells to chemotherapy via induction of apoptosis [119]. The lncRNA PCA3, one of the most clinically validated PCa biomarkers, is highly prostate-specific and detectable in urine, where it has been shown to improve diagnostic specificity compared to PSA [120]. Beyond its diagnostic utility, PCA3 enhances androgen receptor signaling, thereby supporting tumor progression [121]. Similarly, HOTAIR promotes oncogenesis through recruitment of the PRC2 complex and epigenetic silencing of tumor suppressor genes, further reinforcing its link to PCa progression and metastases [122,123]. Their biological roles in PCa tumor microenvironment have highlighted their unique importance in diagnosis and therapeutic options in the treatment of PCa. ncRNAs contribute to the regulation of tumor immunosurveillance microenvironment through the regulation of the expression, development and differentiation of several immune cells including macrophages activation, natural killer cells, dendritic cells, regulatory T cells and cytotoxic T cells, which participate in the PCa cell invasion and metastasis [124].

LINC00675 has emerged as a critical modulator of AR stability in CRPC. Unlike in gastric cancers where it acts as a tumor suppressor, in prostate cancer, LINC00675 expression is elevated and correlates with poor prognosis. Mechanistically, LINC00675 binds to the N-terminal domain (NTD) of the Androgen Receptor, sterically hindering the binding of the E3 ubiquitin ligase MDM2. This blockade prevents ubiquitination and subsequent proteasomal degradation of AR, thereby maintaining high levels of receptor protein even under therapeutic stress. This LINC00675/MDM2/AR axis represents a direct link between the non-coding transcriptome and protein stability networks driving resistance [89]. Downregulation of miR-143, miR-21 and miR-200 have been reported to induce resistant to docetaxel therapy in CRPC via the upregulation of VEGF (vascular endothelial growth factor), which activate KRAS oncogene downstream signaling pathways that promote cell survival while suppressing the apoptotic mediated cell death [125,126]. Using Insilico analysis, Mbeje and colleagues predicted the differential expression of lncRNAs in androgen sensitive (LnCaP) and androgen insensitive prostate cancer cells, where the aberrant expression of lncRNA (TERC) correlates with AR signaling mediated tumorigenesis [127]. This is mediated via the interaction with tumor suppressor miRNAs, which activates TGF signaling that favors tumor progression [127]. Altogether, mis-regulation of ncRNAs is linked to tumor formation through epigenetic modifications including hypermethylation of CpG island promoter leading to the transcription of oncogenic genes that promotes the modification of prostate cancer and progression to CRPC [128].

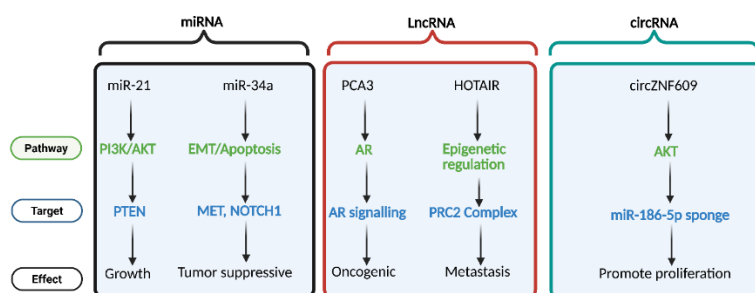


Figure 6. The different classes of non-coding RNAs microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) modulate prostate cancer progression via multiple targets. miR-21 and miR-34a regulate key pathways such as PI3K/AKT and EMT/Apoptosis by targeting PTEN, MET, and NOTCH1,

influencing tumor growth and suppression. lncRNAs PCA3 and HOTAIR modulate androgen receptor (AR) signaling and epigenetic regulation through interactions with the PRC2 complex, contributing to oncogenesis and metastasis. circRNA circZNF609 promotes cell proliferation by acting as a sponge for miR-186-5p, influencing AKT signaling. Pathways (green), molecular targets (blue), and cellular effects (black) are color-coded accordingly.

4. Interplay Between Kinase Signaling and Non-Coding RNAs in Prostate Cancer Progression

Mechanisms that restore AR signaling after ADT therapy are the critical drivers of metastasis and drug resistance in CRPC. Persistent AR signaling due to overexpression, somatic mutations, intra-tumoral androgen biosynthesis, *de novo* androgen synthesis, genomic amplification and altered post-translational regulation is strongly associated with metastatic progression and AR-addicted CRPC [129,130]. AR activity is tightly controlled through post-transcriptional and posttranslational modifications including acetylation, ubiquitination and phosphorylation [131]. These modifications are regulated by the kinase-mediated signaling cascades such as mechanistic target of rapamycin complex-1 (mTORC1), PI3K, protein kinase B (AKT), and mitogen-activated protein kinases (MAPK) which are dysregulated in over 70% of metastatic PCa, compared to about 40% in localized disease. In advanced PCa, treatment with salinomycin inhibits the mTORC/AKT pathway, resulting in loss of AR phosphorylation, downregulation of steroidogenic enzymes CYP17A1 and HSD3 β , and less proliferation of PCa *in vivo* [132]. While the direct phospho-regulation of HSD3 β remains under investigation, compelling evidence demonstrates that MAPK14-mediated phosphorylation of CYP17A1 significantly enhances its 17,20-lyase activity, thereby prioritizing androgen synthesis over mineralocorticoid production.



Figure 7. The Sponge Mechanism of Circular RNAs. Illustration of circular RNA (circRNA) function in the cytoplasm. The closed-loop circRNA structure (gold) confers stability against exonucleases. It functions as a competing endogenous RNA (ceRNA) by containing multiple binding sites for specific microRNAs (red clips). By sequestering these miRNAs, the circRNA prevents them from repressing their target mRNAs (green), thereby effectively upregulating oncogenic proteins.

The concept of lncRNAs acting as sponges for miRNAs is widely cited but rarely scrutinized quantitatively. In the context of lnc-ZNF30-3 and miR-145-5p in prostate cancer, the stoichiometry is critical. For a lncRNA to effectively derepress a target like TWIST1, its abundance must be comparable to the pool of the miRNA it is sequestering. In CRPC, the amplification of the lnc-ZNF30-3 locus often leads to copy number variations that support this high expression level. However, the

sponge effect is likely non-linear; it operates as a threshold mechanism. Below a certain concentration, the lncRNA has no effect on the miRNA-target interaction. Once the lncRNA concentration exceeds the free miRNA pool, a sudden de-repression of TWIST1 occurs, triggering a rapid phenotypic switch to EMT. This digital response mechanism explains the explosive metastatic potential often seen in late-stage disease.

Table 2. The Structural Logic of Kinase Inhibitors in Prostate Cancer.

Inhibitor Class	Binding Conformation	R-Spine State	Mechanism of Action	Resistance Mechanism in PCa
Type I (e.g., Dasatinib)	Active (DFG-in)	Assembled	Binds to the ATP pocket when the kinase is in its catalytically active state.	"Gatekeeper" mutations (e.g., T315I) that sterically block the pocket; upregulation of upstream activators.
Type II (e.g., Cabozantinib)	Inactive (DFG-out)	Disassembled	Stabilizes the inactive conformation by occupying the hydrophobic pocket adjacent to the ATP site.	Mutations that favor the active conformation (R-spine assembly), preventing the inhibitor from binding.
Allosteric (e.g., Trametinib)	Inactive	Disassembled	Binds outside the ATP pocket, preventing the conformational change required for R-spine assembly.	Feedback loop activation of alternative pathways (e.g., PI3K activation following MAPK inhibition).

Previous studies have shown that MAPK14-mediated phosphorylation of CYP17A1 at threonine/serine residues is vital for enhancing its lyase activity and promoting interaction with POR, an important step in androgen biosynthesis [29,133,134]. Given CYP17A1's pivotal role in both classical and "backdoor" androgen biosynthesis pathways, and especially its involvement in intratumoral androgen production in CRPC [1], its dysregulation may contribute to sustained AR signaling, metastatic progression, and resistance to anti-androgen therapy. Upregulation of CYP17A1 expression, combined with the emergence of AR splice variants, has been implicated in resistance to abiraterone, a CYP17A1 inhibitor, by compensating for systemic androgen deprivation [135]. Despite the therapeutic value of targeting CYP17A1, existing inhibitors including abiraterone lack specificity and often affect other steroidogenic enzymes, leading to undesirable side effects such as cortisol suppression [133,136,138]. Hence, more precise approaches are needed, including targeting CYP17A1 post-translational regulation, such as its phosphorylation, or designing non-steroidal small molecule inhibitors to improve efficacy and reduce adverse effects[22]. Phosphorylation of AR itself plays a key role in AR reactivation during CRPC progression. For instance, phosphorylation of AR at Ser81 has been shown to restore AR signaling following ARD1 knockdown, contributing to castration resistance [139]. Inhibition of CYP17A1 using galeterone not only disrupts AR signaling but also promotes degradation of full-length and variant AR isoforms (f-ARVs). Additionally, PI3K-mediated phosphorylation of AR at Ser81 facilitates its recognition and proteasomal degradation via MDM2, a tumor suppressor E3 ubiquitin ligase [140]. A series of mechanistic studies by Tee and Miller

confirmed that MAPK14, a member of the MAP kinase family, phosphorylates CYP17A1 and enhances its lyase activity in non-steroidogenic COS-1 cells, further confirming the enzyme's regulation through phosphorylation [29].

Beyond CYP17A1 and AR, protein kinases broadly contribute to prostate cancer proliferation, metastasis, and resistance to ADT, likely through complex interactions with epigenetic regulators and chromatin remodeling enzymes that influence AR transcriptional programs [141]-[143]. Upon androgen binding, AR translocates from the cytoplasm to the nucleus, where it activates the transcription of androgen-responsive genes (ARGs) that support cancer cell proliferation and survival. Phosphoproteomic profiling has revealed over 10 phosphotyrosine residues on AR in metastatic prostate cancer cells, especially when co-expressed with SRC, a non-receptor tyrosine kinase, supporting the role of hyperphosphorylated AR in driving CRPC [144,145]. Additionally, AKT-mediated phosphorylation of AR at Ser213 and Ser791 enhances prostate cancer cell survival, further implicating kinase pathways in AR regulation [146].

Recent discoveries highlight non-coding RNAs (ncRNAs) including miRNAs and lncRNAs as important regulators of the kinase-AR axis. Their expression is often upregulated in late-stage prostate cancer, where they contribute to therapy resistance and sustained AR activity. Elevated levels of miR-197 and miR-361-3p have been reported in enzalutamide-resistant prostate cancer xenografts [147]. Similarly, LINC01126, a long non-coding RNA induced by ADT, promotes cancer cell survival, recurrence, and metastasis in CRPC. Mechanistically, LINC01126 enhances AR Ser81 phosphorylation, facilitating its nuclear translocation, stabilization, and interaction with cyclin-dependent kinases (CDKs), ultimately worsening disease prognosis [148]. The miR-302/367 cluster, when overexpressed in vitro and in vivo, promotes prostate cancer growth and ADT resistance. However, these effects can be reversed via antisense knockdown or by co-expressing the tumor suppressor LATS2, indicating a phosphorylation-dependent mechanism [149]. Phosphorylation of AR by the MAPK/mTOR/AKT pathway stabilizes its structure and facilitates the recruitment of co-activators, leading to AR hypersensitization in CRPC. Pharmacological blockade of these pathways in preclinical models significantly improves therapeutic outcomes [150]. miR-205 plays an opposing role by disrupting AR co-activator assembly and downregulating AR phosphorylation, making it a potential anti-metastatic agent that limits cell invasion, migration, and growth in prostate cancer [129]. In another example, systemic delivery of miR-124, in combination with enzalutamide, induces cell cycle arrest and promotes apoptosis in prostate tumor cells [151]. lncRNASAT1, a lncRNA associated with supraphysiological androgen levels (SAL), acts as a tumor suppressor in LNCaP cell lines by reducing AKT phosphorylation. In ex vivo patient-derived prostate samples, SAL treatment induces senescence characterized by elevated p16^{INK4}[4]^a and p15^{INK4}[4]^b expression. This senescent phenotype is abolished upon lncRNASAT1 knockdown, indicating its pivotal role in modulating AKT signaling and maintaining SAL-induced tumor suppression [152].

5. Therapeutic Potential and Future Perspectives

Although ncRNAs lack protein-coding ability, they hold significant therapeutic potential in CRPC due to their ability to regulate AR gene expression. Through this regulation, ncRNAs can influence critical cellular processes including proliferation, invasion, metastasis, and the transition from PCa to CRPC often mediated via Wnt/MAPK/mTOR/AKT signaling pathways. For instance, inhibition of miR-182 and miR-744 using siRNA has been shown to drastically suppress the growth of PCa xenografts [110], highlighting their value as potential therapeutic targets. Additionally, Leite and colleagues reported that loss of miR-100-5p facilitates the transition from localized PCa to metastatic disease [153]. miR-100-5p exerts anti-tumor effects by downregulating the mTOR pathway [154], emphasizing its role in key signaling cascades. Interestingly, while miR-100-5p may act as a tumor suppressor, its upregulation has also been observed in androgen deprivation therapy (ADT)-refractory patients at higher risk of relapse post-prostatectomy, suggesting a dual role in the context of ADT resistance [153]. lncRNAs are also central to CRPC pathogenesis. They influence transcriptional and post-transcriptional regulation of AR signaling and are involved in epigenetic

modifications [93,155,156]. Takayama et al. demonstrated that CRPC-associated lncRNAs (CRPC-Lncs) are upregulated in disease and promote AR signaling. siRNA-mediated knockdown of these lncRNAs led to reduced expression of AR variants, splicing machinery, and downstream AR-regulated genes [24]. Other ncRNAs, such as miR-21, have been associated with CRPC aggressiveness. miR-21 represses the expression of tumor suppressors like B-cell translocation gene 2 (BTG2) and PTEN when recruited to AR promoters in androgen-dependent cells [157]. Similarly, miR-12B targets pro-apoptotic genes such as p53, reinforcing its oncogenic role in prostate tumor progression and CRPC development [158]. lncRNAs such as SNHG3, LINC00152, and AK022798 have been implicated in resistance to anti-androgen therapies like enzalutamide by upregulating Notch signaling, thus presenting themselves as crucial therapeutic targets [159].

5.1. Combining Kinase Inhibitors with RNA-Based Therapies

Given the central role of kinase-mediated phosphorylation and non-coding RNAs (ncRNAs) in sustaining androgen receptor (AR) signaling and driving resistance to anti-androgen therapies in CRPC, a novel therapeutic paradigm could involve co-targeting both axes. Specifically, combining kinase inhibitors (e.g., AKT, mTOR, or MAPK14 inhibitors) with RNA-based interventions such as miRNA mimics, antisense oligonucleotides (ASOs), or siRNA constructs may provide synergistic effects by disrupting feedback loops that promote tumor plasticity, androgen biosynthesis, and metastasis [149,160]. For example, miR-205 or miR-124 mimics, when co-administered with kinase inhibitors, could suppress AR phosphorylation, limit co-activator recruitment, and sensitize resistant cells to treatment [160,161]. This dual-targeted approach offers the promise of overcoming acquired resistance and enhancing therapeutic efficacy in patients with advanced disease.

5.2. Advancing Precision Medicine Through Multi-Omics and Functional Genomics

The integration of multi-omics profiling (including transcriptomics, phosphoproteomics, and epigenomics) and CRISPR/Cas9-based functional screens offers powerful tools to identify patient-specific vulnerabilities in prostate cancer. These platforms can reveal oncogenic ncRNAs, essential kinases, or resistance pathways that can be exploited for precision-targeted therapies. For instance, genome-wide CRISPR knockout studies have uncovered synthetic lethal interactions involving AR splice variants, mTOR pathway components, and epigenetic regulators, enabling the design of individualized therapeutic strategies [162]-[164]. Furthermore, integrated omics analysis can stratify patients based on their ncRNA expression signatures, enabling the rational selection of RNA-based or kinase-targeted drugs for tailored intervention.

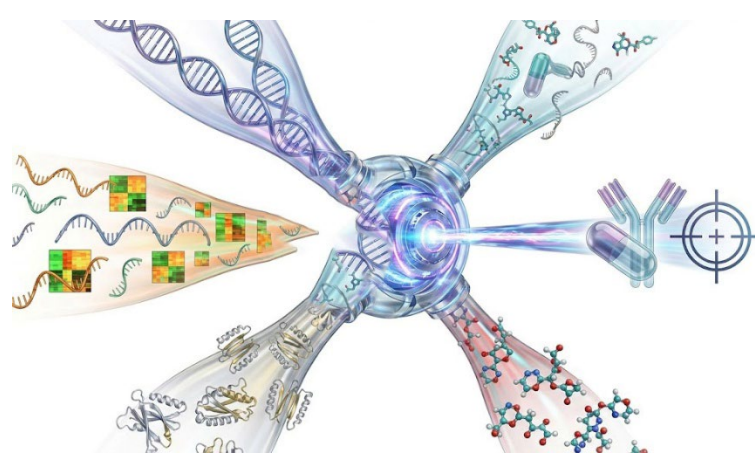


Figure 8. Integrated Multi-Omics Precision Medicine Workflow. A conceptual framework for patient stratification. Data streams from genomics (DNA mutations), transcriptomics (RNA expression), proteomics (protein abundance), and metabolomics are integrated via machine learning algorithms. This multi-dimensional analysis identifies patient-specific vulnerabilities, such as a specific kinase hyperactivity or lncRNA

upregulation, guiding the selection of targeted therapies (e.g., PARP inhibitors, kinase inhibitors) for personalized treatment.

5.3. Nanoparticle-Based Delivery Systems for RNA and Kinase Inhibitors

One of the major limitations of current RNA-based therapies and kinase inhibitors is their poor pharmacokinetics, off-target effects, and limited tumor penetrance. Nanoparticle delivery systems, including lipid nanoparticles (LNPs) and polymeric nanocarriers, offer innovative solutions by protecting nucleic acids from degradation, enhancing cellular uptake, and enabling tumor-specific targeting. Encapsulation of siRNAs targeting CYP17A1 or AR variants, or delivery of kinase inhibitors like AKT/mTOR inhibitors, via ligand-decorated nanoparticles could greatly enhance the selectivity and effectiveness of CRPC treatment [165][167]. Moreover, nanoparticle platforms could be engineered to deliver combination payloads, such as miRNA mimics and kinase inhibitors, in a coordinated and controlled release, further enhancing therapeutic synergy. The efficacy of siRNA therapeutics is contingent upon cytosolic bioavailability, a process heavily dependent on endosomal escape. Lipid Nanoparticles (LNPs) utilize ionizable cationic lipids that become protonated in the acidifying environment of the late endosome (pH ~5.5). This protonation triggers an electrostatic interaction with anionic endosomal phospholipids (e.g., phosphatidylserine), inducing a phase transition from the lamellar bilayer (L α) to the inverted hexagonal phase (H $_{II}$). The H $_{II}$ phase is highly fusogenic, disrupting the endosomal membrane integrity and creating transient pores through which the RNA cargo is released into the cytosol to engage the RISC machinery. Optimizing the pK $_a$ of these ionizable lipids is the current frontier in enhancing the endosomal escape efficiency, which currently remains below 2-5% for standard formulations.

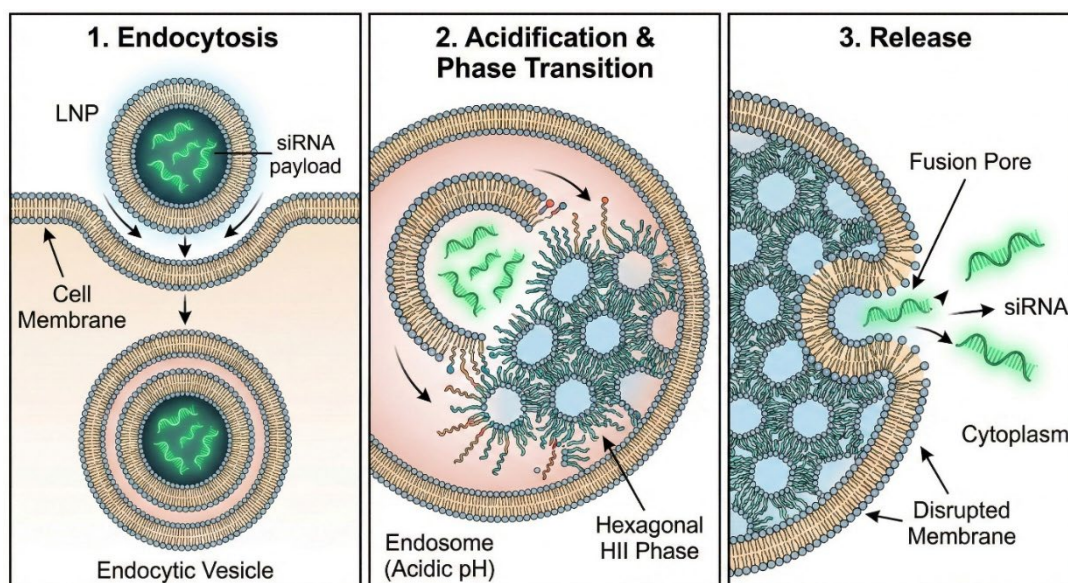


Figure 9. Lipid Nanoparticle (LNP) Endosomal Escape. The physicochemical mechanism of RNA delivery via LNPs. (Left) Endocytosis of the LNP. (Middle) As the endosome acidifies, ionizable lipids within the LNP become protonated, interacting with anionic endosomal lipids to induce a transition from a lamellar bilayer to a hexagonal H $_{II}$ phase. (Right) This membrane disruption creates transient fusion pores, allowing the therapeutic siRNA cargo to escape into the cytosol to engage the RNAi machinery.

5.4. ncRNAs as Biomarkers for Prognosis and Treatment Monitoring

Several ncRNAs, including miR-197, miR-361-3p, miR-205, and LINC01126, have emerged as promising biomarkers for CRPC progression, therapeutic response, and disease recurrence[148,149,160,168]. For instance, elevated circulating levels of miR-197 and LINC01126 have been associated with enzalutamide resistance and poor prognosis. Monitoring the expression of these

molecules in liquid biopsies (e.g., blood or urine samples) could enable real-time tracking of therapeutic efficacy and early identification of resistance phenotypes, thus facilitating timely treatment adjustments. Their incorporation into clinical diagnostic panels may also improve risk stratification and help tailor treatment strategies in a non-invasive, dynamic manner.

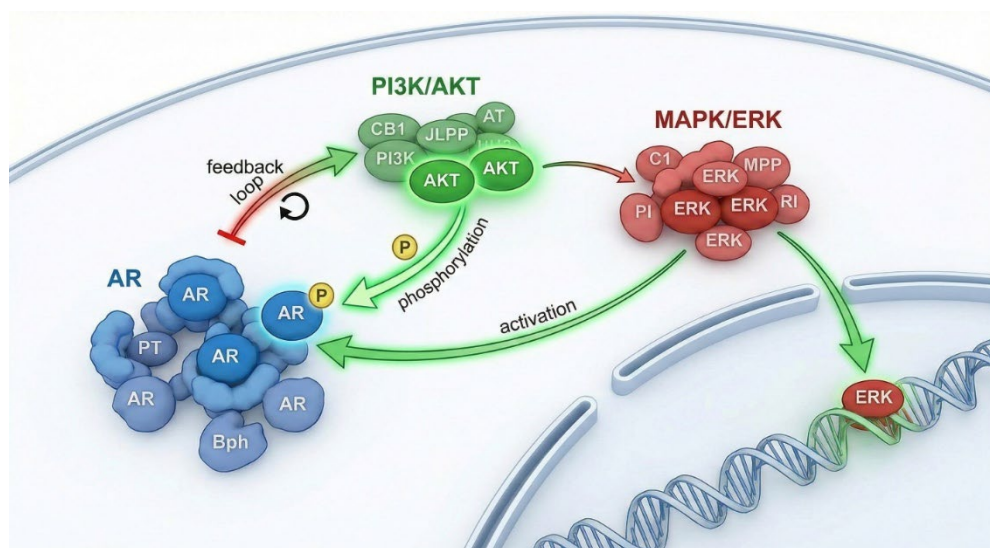


Figure 10. Crosstalk Networks: AR, PI3K, and MAPK. A network topology diagram visualizing the reciprocal feedback loops between major oncogenic pathways. Inhibition of the Androgen Receptor (AR) relieves negative feedback on the PI3K/AKT pathway, leading to compensatory survival signaling. Conversely, activated MAPK/ERK can phosphorylate AR directly, facilitating ligand-independent nuclear translocation. These interconnected nodes illustrate the necessity of combination therapies to prevent adaptive resistance.

6. Conclusion

This review highlights the intricate and multifactorial roles of signaling molecules particularly kinase pathways and non-coding RNAs (ncRNAs) in the development, progression, and therapeutic resistance of prostate cancer, especially in castration-resistant prostate cancer (CRPC). These molecular regulators orchestrate critical events in androgen receptor (AR) signaling, steroidogenesis, tumor cell proliferation, and survival. Beyond being transcriptional "junk," ncRNAs have emerged as functional regulators with roles in chromatin remodeling, mRNA stability, alternative splicing, and post-transcriptional gene silencing [169]. Increasing evidence suggests that miRNAs and lncRNAs directly modulate AR expression and its phosphorylation status, influence the availability of co-activators, and even regulate upstream kinases that control post-translational modifications. This positions them as pivotal nodes within the regulatory circuitry driving therapy resistance and disease aggressiveness. Kinase-mediated phosphorylation of AR and CYP17A1 also contributes to AR reactivation under androgen-deprived conditions, thereby sustaining tumor growth despite treatment. These pathways are frequently upregulated in advanced disease and often interact with ncRNAs, forming feedback loops that complicate therapeutic targeting. Despite these advances, major challenges persist. These include the context-dependent roles of ncRNAs, limited knowledge of kinase-ncRNA crosstalk, off-target effects of current inhibitors, and inter-patient heterogeneity that limits the applicability of standard treatments. In this regard, future research should focus on multi-omics integration, CRISPR-based functional screens, and preclinical validation of candidate ncRNA and kinase targets. Moreover, the development of nanoparticle-based delivery systems for RNA therapeutics and kinase inhibitors, alongside real-time biomarker monitoring through liquid biopsies, holds promise for advancing precision oncology in prostate cancer. A shift toward patient-specific molecular profiling and the co-targeting of both signaling and regulatory RNA networks may

ultimately redefine treatment paradigms and improve outcomes for patients with advanced prostate cancer.

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