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Review Article

Molecular, genetic, and therapeutic advancements in prostate cancer research: a comprehensive literature review

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ABSTRACT

Prostate cancer (PC) is distinguished by its high occurrence among men and is identified as the fifth primary cause of death, with its severity influenced by factors such as age, ethnicity, and genetics. African populations are particularly vulnerable to aggressive forms of the disease. Distinguishing low-risk from high-risk patients remains challenging owing to PC's gradual advancement. While prostate-specific antigen (PSA) detection revolutionized PC diagnosis, it led to overdiagnosis and overtreatment. Despite PSA testing modifications, its specificity remains inadequate. Breakthroughs in genetics and proteomics have introduced fresh biomarkers such as urinary PCA3, leading to the development of pioneering diagnostic assessments like the serum prostate health index (PHI) and 4K score, thereby minimizing the need for unwarranted biopsies. Standard treatments like chemotherapy and prostatectomy are augmented by novel hormone therapies offering better outcomes. Androgen deprivation and hormonal therapy show promise for addressing hormone-sensitive and castration-resistant PC.

Keywords: Prostate cancer, Molecular mechanisms, Genetic factors, Therapeutic strategies

INTRODUCTION

Prostate cancer stands as a significant health concern globally.[1] According to the GLOBOCAN Report 2020 it is the second commonest cancer in males, with total new recorded cases were 1,414,259, and 5th major cause of death after cancer.[2,3] In 2021 globally 2,48,530 cases were reported and the sum of 34,130 deaths.[4] In India, the total number of prostate cancer cases diagnosed in 2020 was 41,532, necessitating a thorough exploration of the current scientific literature.[5] Increased prostate cancer incidence in India is attributed to prostate-specific antigen (PSA) screening, which decreases mortality.[6,7] However, early detection strategies have limitations due to the slow progression of the disease, challenging patient health and longevity. Early diagnosis and treatment plans are essential for reducing mortality rates.[8] PSA screening is recommended for men aged 55 to 69, coupled with DRE for those with elevated PSA levels.[9] The most common PC is adenocarcinoma (90-95%) and more common at over 50 years of age. Risk factors include age, race, ethnicity, dietary habits, obesity, family history, and smoking.[10] Symptoms are often characterized by a painful or weak stream, erectile dysfunction, painful ejaculation, and hematuria.[11] Diagnosis involves systematic prostate biopsy using techniques like transrectal ultrasound/ transperineal or multiparametric magnetic resonance imaging (MRI).[12] Nowadays mpMRI is used to detect prostate cancer (PC) in biopsy-naïve patients.[13] Prostate-specific membrane antigen positron emission tomography (PSMA PET) scan aids in patients with metastatic and post-treatment PSA rise using PSMA ligands like 68 Ga or 18 F.[14] Biomarkers like serum PHI, 4K score, urinary PCA3, EPI, SelectMDx, and MiPS, and tissue ConfirmMDx are utilized for detection.[15] Gleason score grades the tumor.[16] Primary treatments include medical, surgical, and radiotherapy approaches. Grasping these facets is essential for crafting tailored screening and treatment approaches. The goal is to aid future prostate

cancer studies, advancing molecular, genetic, and therapeutic research. This review supports evidence-based clinical decisions, pinpointing gaps in current knowledge. Addressing these gaps is crucial for better patient outcomes and guiding future research. By filling these voids, we can improve clinical practice and patient care. The review is a resource for researchers, clinicians, and policymakers, guiding research questions and methodologies for progress in the field.

METHODS

This literature review aims to analyze current scientific knowledge focusing on prostate cancer extensively. Key objectives include demonstrating breadth and depth of understanding, critically appraising existing literature, identifying research gaps, and justifying the significance of addressing these gaps. The review covers three main themes: molecular mechanisms, genetic factors, and therapeutic treatment of PC. For the literature review, searches were conducted across multiple databases including PubMed, Web of Science, Embase, Medline, and the Cochrane central register of controlled trials, covering studies published up to 31 December 2023. A total of 160 series were identified, with 75 deemed relevant to the study's focus. Additionally, manual searches of article reference lists were performed. The search terms employed included "prostate cancer," "prostate carcinoma," "molecular biology," "genetic factors," "genetic mutations," "gene expression," "genetic predisposition," "biomarkers," "molecular targeted therapy," "immunotherapy," "precision medicine," "genetic profiling," and "therapeutic advancement." Various search strategies utilizing Boolean operators (and, or, not) such as "prostate cancer" and "molecular biology," "prostate carcinoma" and "genetic mutations," and "therapeutic interventions" and "precision medicine" and "prostate cancer" were employed. Medical subject headings (MeSH) terms were utilized in PubMed or other MeSH-indexed databases. The search and selection procedures are compiled with the recommendations outlined in the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines. Exclusions were made for irrelevant topics, studies lacking full-text availability, or those with insufficient data. Additionally, a manual review of datasets was conducted to identify duplicate entries or data points.

THEME 1

Unravelling molecular mechanisms in prostate cancer

This section meticulously examines the molecular complexities implicated in the onset and advancement of prostate cancer. Subheadings explore and analyze androgen receptor signalling pathways, tumor suppressors, and the tumor microenvironment's role. Molecular events such as angiogenesis and the epithelial-mesenchymal transition are scrutinized to assess their impact on disease progression.

1A

Prostate cancer and androgen receptor signalling pathway

The androgen receptor (AR) plays a central role in prostate cancer (PC), being essential for both the advancement of the disease and the maintenance of normal male reproductive function. AR interaction with androgens triggers Hsp90 separation, facilitating AR nuclear translocation.[17] Altered AR activity or aberrant androgen levels propel the evolution and advancement of prostate cancer. Initially, prostate cancer cells exhibit AR positivity, but in later stages, they become AR-negative and less specialized.[18] Shorter glutamine (CAG) repeats in AR's transactivation domain elevate PC risk.[19] Increased levels of histone methyltransferase DOT1L in prostate cancer enhance the expression of AR through c-MYC, by inhibiting c-MYC-controlled E3 ubiquitin ligases.[20] AR, working in tandem with NCOA2, stimulates prostate cancer cell growth and spread through the PI3K/MAPK pathways, regardless of AR's direct interaction with DNA. When AR interacts with p85a, it enhances AKT kinase activity through PIP3, promoting the development of castration-resistant prostate cancers.[21] FOXA1, GATA2, and OCT1 enhance the binding of AR to DNA, correlating with the advancement of prostate cancer.[22] Dysregulated AR signalling influences target genes like PSA, FGF8, CDK1, TMPRSS2, and PMEPA1, fuelling PC progression and metastasis.[23] Genetic alterations in AR variants (AR-V1, AR-V7, AR-V567) are associated with castration-resistant PC and poor survival.

1B

WNT/beta-CATENIN signalling pathways

It plays an important role in PC by activating tyrosine kinase-like orphan receptors 1 [ROR 1], especially in castrate-resistant PC [CRPC].[24] Elevated levels of the WNT carrier protein Wntless (WLS) in tumor cells are associated with the activation of the WNT/beta-CATENIN route in primary prostate cancer, particularly in castration-resistant prostate cancer (CRPC).[25] The WNT pathway, particularly Wnt5A, plays a significant role as cells migrate through the bloodstream. These tumorigenic cells, supported by WNT/beta-CATENIN signaling, utilize CHD11, CD24, and Wnt5A to facilitate prostate cancer-related bone metastasis.[26]

1C

Phosphoinositide 3-kinase pathway (PI3K/AKT)

The relationship between PI3K and prostate cancer (PC) is well-established. PI3K-C2BETA, a class 2 PI3K isoform, controls ERK1/2 and MEK1/2 activity, influencing PC cell migration and invasion.[27] Activation of AKT stimulates the progression of prostate cancer cells via the MAPK pathway. MAPK4 governs AKT activity through the

caspase 4/5-dependent pathway, resulting in the degradation of GATA2, which subsequently modulates AR activity.[28] The PI3K/AKT/NF-Kb/BMP/SMAD pathway supports prostate cancer invasion and the spread of cancer to the bones.[29] Decreased expressions of PLK4 and PI3K signaling in prostate cancer inhibits cell proliferation, migration, invasion, and metastasis.[30] Targeting the c-MYC/PI3K/AKT/mTOR axis can hinder tumor progression.[31] PTEN inhibits PIP3 formation, and its loss leads to PI3K pathway overexpression.

1D

JAK/STAT pathway

This pathway is linked to prostate cancer in terms of tumor advancement, angiogenesis, and metastasis, mainly because of the secretion of cytokines like interleukin 6 (IL6) and its interaction with PI3K and MAP kinase pathways.[32]

1E

Other factors like microRNAs [miRNA], and small noncoding RNAs, are involved in PC development and metastasis.

Highlighting the interplay between AR signaling and cellular processes shapes prostate cancer biology. Oncogenes like MYC/PTEN and tumor suppressors such as TP53 play pivotal roles in prostate cancer pathogenesis. Dysregulation of these genes contributes to disease development and progression, offering targets for therapy. Molecular events like angiogenesis and EMT drive metastasis by promoting tumor growth through the formation of new blood vessels and enhancing cancer cell migration and invasion respectively. Analyzing these processes aids in understanding disease progression and identifying therapeutic targets. Addressing conflicting findings and exploring emerging research challenges in targeted therapy underscore the need for more effective treatment strategies. Understanding these complexities is crucial for advancing the field and developing more effective treatment strategies.

THEME 2

Deciphering genetic factors in prostate cancer

This theme delves into the genetic landscape of prostate cancer, covering both germline and somatic mutations. Understanding the genetic basis of inherited prostate cancer remains a challenge. One of the key risk factors for prostate cancer is a familial history of the condition, especially if an immediate family member like a father or brother is diagnosed before turning 65. The risk escalates for individuals with two first-degree relatives affected by prostate cancer, leading to a five-fold increase in risk. Moreover, those with a strong family history are prone to developing the cancer earlier and with more severe manifestations. Additionally, they face heightened chances of experiencing biochemical recurrence following surgery. This highlights that hereditary prostate cancer (HPCa) results from gene mutations passed down in an autosomal dominant pattern, leading to early-onset cases.

HPCa incidence is two to three times higher in African American men than in European and Asian men. Family history serves as a robust indicator, with inherited mutations believed to contribute to approximately 9% of all cases and a substantial 45% in men below 55 years old.[33] Various studies have pinpointed multiple chromosomal regions correlated with inherited prostate cancer, including 1q24-25, 1q42.2-43, 1p36, Xq11, Xq27-28, 20q13, and 11p, yet the specific genes involved remain largely unidentified.[34] Although mutations in the RNASEL gene at 1q24-25 have been associated with certain families affected by hereditary prostate cancer (HPC-1), they are not prevalent across all instances.

Similarly, the gene HPC2/ELAC2 on chromosome 17p has been associated with increased risk, but its role in causing prostate cancer is unclear. Efforts to identify predisposing genes have included linkage mapping studies of affected siblings. In one study, approximately 600 affected sibling pairs were analyzed, revealing chromosome 16 as a potential locus of interest, particularly when certain clinical factors were considered.

Subsequent sequence analysis of two candidate genes within this region, 17β-HSD and KIAA 0872, did not find causative mutations. Further sequencing within this region is needed to uncover the specific DNA sequences underlying prostate cancer susceptibility.

2A

Men harboring specific inherited mutations in breast cancer genes (BRCA), including BRCA1, BRCA2, ataxia telangiectasia mutated (ATM), checkpoint kinase 2 (CHEK2), partner and localizer of BRCA2 (PALB2), mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), and MSH6, confront an increased likelihood of prostate cancer development. Nonetheless, there is a deficiency in precise screening protocols for individuals with these mutations.[35] Remarkably, mutations in the BRCA2 gene are closely associated with a heightened susceptibility to aggressive prostate cancer, with the risk elevated between 2.5 to 8.6 times by the age of 65.

2B

Lynch syndrome

Genetic alterations impacting DNA mismatch repair genes can also give rise to prostate cancer. For example, mutations in the epithelial cellular adhesion molecule gene (EPCAM) induce methylation of the MSH2 promoter, resulting in the depletion of MSH2 protein, resembling Lynch syndrome.[36]

Moreover, mutations in the HOXB13 gene are linked to prostate cancer development.[37] Additionally, mutations in the CHEK2 gene are correlated with a heightened propensity for prostate cancer.[38]

2C

Numerous genetic mutations are associated with advanced prostate cancer that spreads and becomes resistant to treatment. The PIK3CA oncogene mutations are commonly found in different cancer types, including prostate cancer (PC). Mutations occurring within the KIT, BRAF, and TP53 genes are linked to late-stage cancer and unfavorable prognoses. Targeting tumors with KIT mutations has shown effectiveness through the use of BRAF inhibitors and tyrosine kinase inhibitors.[39,40] Specific instances of prostate cancer are connected to genetic mutations in genes like zinc phosphodiesterase ELAC protein 2 and histone promoter control protein 2 (HPC2).[41] Additionally, alterations in the RNASEL gene are linked to the early onset of prostate cancer and the formation of aggressive tumors. RNase L gene functions in cancer prevention by breaking down RNA.[42] The absence of retinoblastoma 1 (RB1) and TP53 enhances cell proliferation, reduces androgen receptor signaling, and promotes aggressive tumor growth that is resistant to treatment with AR antagonists, resulting in a bleak prognosis. In such instances, targeted molecular therapy is advised.[43] Mutations in PALB2 and inactivation of CDK12 are implicated in the progression of aggressive tumors that demonstrate resistance to hormone therapy and poly ADP-ribose polymerase inhibitors (PARPi). To tackle this obstacle, utilizing immunotherapy involving programmed cell death protein 1 (PD-1) blockers is suggested as a viable treatment approach.[44]

The review highlights the importance of genetic markers in risk assessment and personalized treatment for prostate cancer. Individuals with BRCA gene mutations and Lynch syndrome are at higher risk, but screening guidelines for these high-risk groups are lacking. Challenges in risk assessment and screening underscore the need for personalized approaches to identify at-risk individuals. Specific genes like BRCA1, BRCA2, and HOXB13, along with common genetic variants, contribute to prostate cancer risk. Defects in DNA repair pathways, often associated with germline mutations, increase susceptibility to prostate cancer. Understanding familial predisposition and DNA repair efficiency aids in assessing disease risk. The prognostic significance of genetic alterations refines risk assessment models, enabling tailored therapies.

THEME 3

Therapeutic strategies in prostate cancer: current status and future directions

Exploring the latest advancements in prostate cancer treatment, this subheading focuses on novel therapeutic agents. This section critically evaluates current therapeutic modalities, including active surveillance, hormone therapy, surgery, radiotherapy, chemotherapy, immunotherapy, checkpoint inhibitors, and challenges posed by treatment resistance.[45] The treatment approach for prostate cancer hinges on whether the goal is to achieve a cure or to manage symptoms, considering accompanying medical conditions, associated co-morbidities, and the individual's life expectancy. Because of the rapid change in options for PC treatment, we cannot arrange in order one after another.

3A

Active surveillance

Grade group 1 disease, characterized by low volume and slow progression, poses low risk with a life expectancy of less than 5 years. Management includes periodic PSA testing, digital rectal examination (DRE), and biopsies conducted at regular intervals.[46]

3B

In the nascent phase of prostate cancer, around 80-90% of cases demonstrate elevated androgen activity. Reduction in androgen level is a mainstay in PC treatment making androgen deprivation therapy (ADT) a first-line treatment option for hormone-sensitive prostate cancer. 20-30% of PCs show recurrence after ADT and develop castration-resistant prostate cancer (CRPC) and mCRPC.[47]

3C

For localized disease, we do close monitoring, radiotherapy (RT), and radical prostatectomy (RP) through open-retropubic and transperineal, laparoscopic, and robotic-assisted techniques. RP is a first-line treatment and reduces mortality. Side effects of RP are urinary incontinence and sexual dysfunction. Focal therapy, which encompasses techniques like cryoablation and high-intensity focused ultrasound (HIFU), is utilized for treating small, low-risk tumors in prostate cancer. However, its efficacy is currently under investigation.[48]

3D

Metastatic disease is treated with chemo-hormonal therapy and cell-based cancer immunotherapy.

Recently used treatment for prostate cancer

Novel hormone therapy

It affects the androgen signaling pathway to suppress androgen levels also known as ADH.[49] ADH comprises-antiandrogens which are of two types steroidal-cyproterone acetate (CPA), nonsteroidal (bicalutamide, flutamide, nilutamide), long-acting LHRH agonist (leuprolide, triptorelin), LHRH antagonist (Abarelix, Degarelix, oral Relugolix). Abiraterone and enzalutamide

have regulatory approvals for PC. Abiraterone is a selective inhibitor of cyproterone p450 17A1 (CYP17) which causes androgen reduction by targeting the androgen pathway and is approved for mCRPC patients.[50] Enzalutamide, darolutamide, and apalutamide, advanced antiandrogens endorsed for nonmetastatic CRPC patients, also decrease metastatic progression and mortality rates by 71%.[51] In November 2023, Enzalutamide garnered FDA approval for treating nonmetastatic castration-sensitive prostate cancer (nmCSPC), permitting its utilization with or without GnRH analog therapy. This endorsement particularly aims at patients facing biochemical recurrence and those identified as high risk for metastasis. The prevalent adverse effects of ADH include Gynecomastia, breast discomfort, gastrointestinal issues, fatigue, and hot flashes.

Chemotherapy

Docetaxel functions by hindering microtubule assembly in both mitosis and interphase, leading to cell demise. Cabazitaxel is employed as a subsequent therapeutic option for prostate cancer. Furthermore, Mitoxantrone, another secondary medication, prompts immunogenic cell death by activating eukaryotic initiation factor 2.[52] Side effects are cytopenia, nausea, vomiting, neutropenic sepsis, fatigue, and shortness of breath.

Radiotherapy

It's utilized for managing locally advanced conditions and curtailing metastasis. External beam radiation therapy (EBRT) employs techniques like 3-D conformal radiation therapy, intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), stereotactic ablative body radiotherapy, and volumetric modulated arc therapy (VMAT) brachytherapy. Radium 223 is specifically administered to patients with mCRPC featuring bone metastases, given intravenously over four weeks for six cycles.[53] Typical adverse effects include bone discomfort, fatigue, gastrointestinal issues, hematological toxicity, thrombocytopenia, and leukemia.

Phototherapy

Thermal energy is employed to prompt apoptosis in cancer cells through the utilization of materials capable of absorbing electromagnetic energy and converting it into thermal energy. This method poses a lower risk of infection and presents fewer side effects compared to chemotherapy. Near-infrared light, specifically in the range of 800-1350 mm, is predominantly utilized for this purpose in photothermal therapy (PT).[54] This can be blended with other therapies like radio or immunotherapy to enhance its impact against tumors.

Immunotherapy

It shows promise in prostate cancer therapy, although its precise effects are still being fully understood. It operates through both active and passive methods. The active approach involves vaccines that enhance immune response by presenting antigens, while the passive approach employs monoclonal antibodies targeting tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). In prostate cancer, vaccine effectiveness can be evaluated using specific biomarkers such as early detection of cancer recurrence, slowed tumor growth, and a range of TAAs (e.g., PSA, PSMA), TSAs, prostate stem cell antigen (PSCA), prostate acid phosphatase (PAP), PCA3 antigen, and mucin-1. Vaccines can be combined with radiotherapy and chemotherapy. They are categorized into two groups: cell-based and viral vector-based vaccines.[55] Recently, chimeric antigen receptor (CAR) T-cell immunotherapy has been applied to solid tumors, where antibody fragments are utilized alongside T-cells targeting TSAs. Several new TAAs are currently being investigated, including immune checkpoint B7-H3 (CD276), mucin-1, IL-6 receptor (CD126), Lewis-y antigen, and STEAP-1. These represent emerging and effective treatment options for metastatic castration-resistant prostate cancer (mCRPC).

Cell-based vaccines

1-Sipuleucel-T is an autologous dendritic cell therapy that enhances the immune response against the PAP antigen. It proves advantageous for managing mildly symptomatic prostate cancer. This vaccine marks the first FDA approval in the United States, administered in three doses at two-week intervals via intravenous infusion. Common side effects include bleeding, bruising, fever, fatigue, nausea, and headache.

G-VAX

This vaccine involves the transfer of the granulocyte-macrophage colony-stimulating factor (GM-CSF) gene into tumor cells. It induces the activation of various tumor-associated antigens (TAAs) without requiring HLA matching. Viral vector-based vaccines of type B are derived from oncolytic viruses. They function by infecting tumor cells, prompting their demise, and activating antigen-presenting cells (APCs). These APCs then generate tumor-associated antigens (TAAs) responsible for triggering T-cell responses. However, findings from the PROSTVAC-VF study indicate limited efficacy of this vaccine.

Immune checkpoint inhibitors

Within the tumor microenvironment (TME), tumor cells coexist with an assortment of immune cells, spanning myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), and tumor-associated dendritic cells (tDCs), alongside adaptive immune cells like regulatory T cells (Tregs). This complex milieu, comprising cellular and soluble constituents, promotes tumor progression and enables evasion from immune surveillance. Immune

checkpoint inhibitors (ICIs) are designed to address receptors responsible for regulating immune responses, effectively counteracting the suppressive effects of the tumor microenvironment (TME) on immunity. Clinically validated ICIs that target PD-L1, PD-1, and CTLA4 have shown notable effectiveness. In prostate cancer (PC), there's a notable presence of high PD-1/PD-L1 expression, where PD-1 interacts with PD-L1 in tumor cells, promoting immune evasion. Mutations in CDK-12 correlate with increased immunotherapy sensitivity, while insufficient mismatch repair is a universal indicator for anti-PD1 therapy. The combination of anti-PD-1/PD-L1 and anti-CTLA-4 agents has demonstrated synergistic effects in specific cancer types. CTLA-4 receptor inhibition via agents like Ipilimumab holds promise in PC treatment, particularly in metastatic castration-resistant prostate cancer (mCRPC). Antiangiogenic agents also modulate the TME, enhancing responses to ICIs by countering immunosuppression. Preclinical studies reveal PD-L1 overexpression induced by poly (ADP-ribose) polymerase (PARP) inhibitors. A PARP inhibitor blocks the action of an enzyme called PARP, crucial for DNA repair in cells. Olaparib and Rucaparib, two such inhibitors, have been shown to enhance the sensitivity of natural killer (NK) cells in prostate cancer. These inhibitors are approved for use in specific cases where prostate cancer displays particular genetic defects, has spread to other parts of the body, and has become resistant to standard hormone treatments. The interplay between the immune response and angiogenesis in the TME creates an environment that suppresses immune activity. Antiangiogenic agents have the additional effect of modulating the immune system, making it more responsive to immune checkpoint inhibitors (ICIs). Notably, pembrolizumab and dostarlimab, two ICIs, have received approval for treating various tumors, including those found in prostate cancer cases with specific genetic characteristics.

Gene therapy

Gene therapy (GT) in PC involves the transfer of genetic material into cancer cells to modulate gene expression, inhibiting tumor growth and metastasis. This involves advanced drug delivery systems and focuses on suicide gene therapy (SGT), tumor-suppressor gene therapy (TSGT), anti-oncogene therapy (AOT), and immunomodulatory gene therapy (IGT). SGT introduces therapeutic genes to induce cancer cell death, with enzyme-based approaches like gemcitabine-conjugated adenovirus showing promise. TSGT introduces wild-type genes (e.g., p53, p21, retinoblastoma) to inhibit tumor growth. The protein p14ARF, regulating AR activity, and miR-21 targeting PTEN have been employed for tumor suppression in the prostate. IGT enhances the immune response against tumors through gene vaccines and intra-tumoral cytokine genes using vector injections, addressing immune deficiencies in PC. AOT inhibits tumor growth without damaging normal cells by targeting specific tumor RNAs, often conjugated with therapeutic genes like adenovirus early region-1 for safe transgene delivery, showing potential in PC treatment.

Nanotherapies

Nanotechnology has revolutionized disease treatment and diagnosis, particularly in cancer eradication, through targeted drug and gene delivery using nanocarriers. These carriers, including polymeric spheres, liposomes, dendrimers, carbon nanotubes, and mesoporous silica nanoparticles, enhance drug delivery with improved biocompatibility. Nanocarriers are evolving for tumor marker detection, employing aptamers due to their low immunogenicity and easy synthesis. Self-assembled polymeric nanoparticles, incorporating PLGA and PEG and functionalized with the Wy5a aptamer, effectively suppress prostate cancer (PC) aggression. These doxorubicin-loaded nanostructures effectively eradicate PC and delay tumor growth in xenograft models. Aptamer modification enhances their internalization into PC cells. Additionally, hyaluronic acid-modified nanoparticles carrying epigallocatechin-3-gallate significantly reduce PC proliferation rates. RNA interference (RNAi) is utilized for gene silencing, with nanocarriers enhancing RNAi internalization. Gold nanoparticles loaded with siRNA penetrate PSMA-overexpressed PC cells. Mesoporous silica nanoparticles improve siRNA gene-silencing potential. PLGA-based nanocarriers deliver androgen receptor-shRNA, aiding in PC suppression Down-regulation of the Lcn2 gene increases tumor cell sensitivity to cisplatin. Clinical research validates the efficacy of diverse nanocarriers in transporting therapeutic substances to PC cells. Anthracyclines, platinum-based compounds, and polypeptide-based nanocarriers containing doxorubicin demonstrate potential in impeding PC metastasis. Additionally, studies have demonstrated that the use of CRISPR/Cas9 technology to delete interleukin-30 reduces prostate cancer growth and extends progression-free survival. This effect is achieved by increasing SOCS3 levels and inhibiting the expression of IGF1 and CXCL.

Targeted radiation therapy and PSMA

Scientists have created precision therapies leveraging PSMA, the protein used in imaging prostate cancer. These therapies involve chemically combining a molecule that targets PSMA with a radioactive compound. This novel compound shows promise in locating, binding to, and eradicating prostate cancer cells throughout the body.

Recent clinical studies have yielded encouraging outcomes, demonstrating that individuals with advanced prostate cancer who were treated with a drug targeting PSMA survived longer than those subjected to conventional treatments. Consequently, the FDA has granted approval for the medication Lu177-PSMA-617 (Pluvicto) to be used in specific cases of metastatic castration-resistant prostate cancer (mCRPC) in individuals who test positive for PSMA.

Continuing and forthcoming clinical investigations are assessing the effectiveness of drugs that target PSMA in individuals with initial stages of prostate cancer, alongside their potential synergies with other treatments like PARP inhibitors and immunotherapy.

Newer therapies under trial

It includes: neoadjuvant androgen deprivation therapy (NADT) for T1 and T2 disease before radical treatment; custirsen (cytoprotective chaperon) and chemotherapy combination is in phase 3 trials; neoadjuvant chemoharmonal therapy with Docetaxel and complete androgen blockade is under phase 2 trials for locally advanced high-risk prostate cancer; and sunitinib (multikinase inhibitor) for prostate cancer is also safe and effective prior to radical treatment.

RECOMMENDATIONS FOR FUTURE RESEARCH DIRECTIONS

This comprehensive overview assesses each modality's strengths and limitations in different stages of prostate cancer. Whether targeting specific molecular pathways, exploiting genetic vulnerabilities, or employing innovative delivery systems, this section critically analyzes emerging agents that show promise in preclinical and clinical settings. The potential advantages and challenges associated with these novel agents are thoroughly examined. Critical evaluation of the clinical outcomes, challenges, and ongoing research in immunotherapy for prostate cancer sheds light on its role in the evolving landscape of cancer treatment. Addressing a significant hurdle in prostate cancer management, this subsection delves into the challenges posed by treatment resistance. Whether resistance arises from androgen deprivation therapy, chemotherapy, or other modalities, a critical analysis of the underlying mechanisms provides insights into potential strategies to overcome resistance. The review discusses ongoing research efforts to elucidate and combat resistance in prostate cancer treatment. An in-depth analysis of recent clinical trial results offers insights into the present landscape of therapeutic investigations in prostate cancer. This includes the assessment of new drugs, treatment combinations, and innovative approaches. The review analyzes the implications of trial results on clinical practice and highlights areas where further investigation is warranted. This subheading explores the integration of precision medicine in urological oncology, with a focus on its application in prostate cancer.

CONCLUSION

In conclusion, this literature review provides a comprehensive overview of prostate cancer research, emphasizing breadth and depth of knowledge. Critical appraisal of molecular mechanisms, genetic factors, and therapeutic strategies reveals current gaps in understanding. Recommendations for future research directions underscore the importance of addressing these gaps to advancement in the field of urology and improved outcomes for prostate cancer patients.

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