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Review

Nanotherapy to Reshape the Tumor Microenvironment: A New Strategy for Prostate Cancer Treatment

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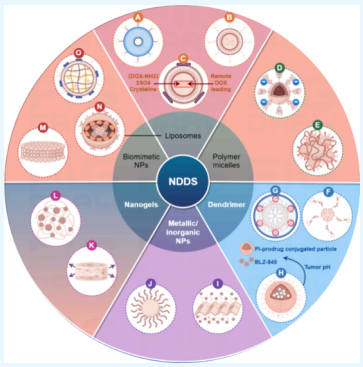
ABSTRACT: Prostate cancer (PCa) is the second most common cancer in males worldwide. Androgen deprivation therapy (ADT) is the primary treatment method used for PCa. Although more effective androgen synthesis and antiandrogen inhibitors have been developed for clinical practice, hormone resistance increases the incidence of ADT-insensitive prostate cancer and poor prognoses. The tumor microenvironment (TME) has become a research hotspot with efforts to identify treatment targets based on the characteristics of the TME to improve prognosis. Herein, we introduce the basic characteristics of the PCa TME and the side effects of traditional prostate cancer treatments. We further highlight the emergence of novel nanotherapy strategies, their therapeutic mechanisms, and their effects on the PCa microenvironment. With further research, clinical applications of nanotherapy for PCa are expected in the near future. Collectively, this Review provides a valuable resource regarding the various nanotherapy types, demonstrating their broad clinical prospects to improve the quality of life in patients with PCa.



1. INTRODUCTION

Epidemiological data emphasize that prostate cancer (PCa) is a global health issue with a high incidence and considerable impact on patient quality of life. The cancer forecast data released by the American Cancer Society in 2022 predicted that approximately 260,000 new cases of PCa would be diagnosed in the United States alone, accounting for 27% of all male cancer cases.[1] Various risk factors contribute to the development of PCa, including age, heredity, and ethnicity. Androgen deprivation therapy (ADT) has long been a pillar of PCa treatment, with effective androgen synthesis and antiandrogen inhibitors successfully developed for clinical use. However, long-term hormone deprivation and androgen receptor (AR) ablation increase the incidence of ADT-insensitive PCa and poor prognosis. Surgical resection is another primary treatment modality for PCa; however, its success rate is limited by many factors, often requiring adjuvant therapies such as radiotherapy and chemotherapy. The PCa tumor microenvironment (TME), similar to that of several other tumors, is acidic and hypoxic, rendering traditional treatments ineffective. Additionally, traditional treatments damage normal tissues with limited therapeutic effects in patients with advanced PCa. Although patients with localized PCa have a high long-term survival rate, metastatic PCa is difficult to cure even with aggressive treatment. The high fatality rate associated with advanced disease can be attributed to the absence of effective treatments capable of generating a durable response in cases characterized by significant tumor heterogeneity at the genetic and cellular levels. Therefore, investigating novel therapeutic approaches for this condition is imperative.

The gradual evolution of prostate tissue from benign tumors to malignant lesions or distant metastases is driven by apparent intracellular transmission changes and TME remodeling. Thus, the TME critically influences the development, advancement, and metastasis of PCa, representing an important therapeutic target. As metastatic PCa shows a limited response to immune checkpoint inhibitors, it is considered an "immune-cold" cancer.[2] Transforming the metastatic TME into an antimetastatic TME is a treatment strategy to prevent local PCa cells from spreading to other organs.[3] Nanotherapy has attracted substantial research attention as a strategy to overcome the limitations of traditional therapeutics and target the TME. Indeed, nanoparticles (NPs) facilitate targeted drug delivery and release in the TME. NPs represent a potentially effective treatment option for PCa in particular due to their ability to passively target solid tumors via tumor-enhanced permeability and retention effects. Moreover, owing to their small size, NPs improve the efficiency of anticancer drug loading, actively target tissues via binding to receptor-targeted molecules, and are not associated with the side effects elicited by systemic

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nontargeted therapy.[4] This article discusses the roles and effects of different types of nanotherapy in remodeling the TME of PCa while also emphasizing the potential of nanotherapy to improve treatment outcomes for patients with PCa.

2. PROSTATE CANCER AND ITS MICROENVIRONMENT

2.1. Overview of the Prostate and PCa. The prostate is the largest accessory gland in men, located deep in the pelvic cavity, directly inferior to the bladder, anterior to the rectum, and wraps around the urethra.

During embryonic development, the stroma and epithelium continuously interact. In adolescence, androgen and estrogen production stimulates stromal activity, promoting epithelial growth, proliferation, and secretory activity in the development of the prostate, which continues throughout adulthood.[5] Moreover, as secondary sex characteristics begin to develop in men, the pituitary gland stimulates testes growth. Meanwhile, in addition to producing sperm, the testes begin secreting high levels of male hormones, which feedback to stimulate prostate growth. Therefore, normal testes function is a requisite for normal prostate development.

Human and mouse prostates exhibit anatomical variances yet share certain cellular similarities. In particular, transcriptome mapping has revealed that the murine dorsolateral prostate is analogous to the peripheral region of the human prostate, the site where ∼60−75% of human PCa cases initially develop. Moreover, human and murine prostates comprise three types of epithelial cells: basal, luminal, and neuroendocrine cells. Prostatic tumors derived from luminal cells exhibit greater aggressiveness and are associated with a poorer prognosis than those derived from basal cells. Additionally, prostate tumor subtypes with basal stem cell characteristics are associated with more aggressive forms of PCa. However, a large prospective study of these features is required to determine their importance as prognostic biomarkers.

Other cell types in the prostate epithelium, including fibroblasts, smooth muscle cells, endothelial cells, and immune cells, can also significantly impact the behavior of PCa.[6] Although gene mutations in normal epithelial cells are the main factors affecting PCa development, identifying the specific variables responsible for its development and progression is challenging due to the complex etiology and tumor heterogeneity. Nevertheless, the mutual effects of malignant epithelial cells and the TME in driving PCa progression have been partially characterized, revealing the intricate cross-talk between cancer cells and the various TME components. That is, cancer cells promote tumor occurrence and progression through autocrine and paracrine modifications and specific cellular responses to maintain their survival and development. According to the Gleason score, prostate-specific antigen (PSA) levels, tumor, node, metastasis (TNM) stage, and other indices can be used to preliminarily diagnose PCa, predict prognosis, and establish treatment strategies.

2.2. Traditional PCa Treatments and Limitations. PCa treatment has improved markedly over the past 15 years. However, most treatment regimens include nonspecific chemotherapeutic drugs or drugs that further inhibit AR signals. While radical prostatectomy can directly eliminate the PCa, it is associated with certain adverse effects, including a significant reduction in testosterone levels and a corresponding decrease in libido. Consequently, due to the notorious slow progression of PCa, many males elect not to undergo surgery. Nevertheless, no clinical tools are capable of accurately predicting the timing of PCa cell migration from the prostate to other sites, i.e., metastasis, during active monitoring. The liver, bones, and lymph nodes are the most frequently affected sites of PCa metastasis. Although local tumors can be treated, approximately one-third of patients experience relapse, of whom one-third ultimately succumb to PCa. Moreover, while ADT has been the cornerstone of metastatic PCa treatment for more than 60 years, however, castration-resistant precancerous adenocarcinoma (CRPC) often occurs within three years of initiating ADT, with metastatic (m)CRPC representing the most fatal stage of the disease.[7]

Considering the inability of traditional treatment modalities to prevent PCa metastasis and the various associated adverse side effects, including urinary incontinence, erectile dysfunction, fatigue, bowel issues, and hormone fluctuations, the need for new, safe, and effective therapeutic strategies for PCa has become increasingly urgent.

2.3. Definition of the TME. The TME is a complex environment comprising cancer cells, blood vessels, extracellular matrix (ECM), and immune cells (Figure 1). Within the

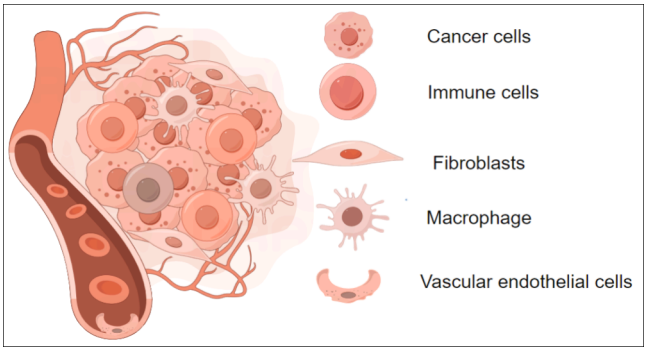

Figure 1. Composition of tumor microenvironment. The tumor microenvironment consists of various cell types, including tumor, immune, epithelial, and stromal cells. Created with figdraw.com. License ID: PSAAP4a390.

TME, cancer cells and surrounding noncancer cells mutually interact and engage in cross-talk, influencing tumor formation, development, and therapeutic response. Although the specific composition and characteristics of the TME may differ among tumor types, the major constituents include tumor cells, ECM, cancer-related fibroblasts, blood vessels, and immune cells. The clinical heterogeneity of anterior adenocarcinomas, including PCa, is reflected in the spatial and clonal genetic diversity. Malignancy is predominantly driven by cancer cells, which are profoundly influenced by the activity of the ECM and regulated by myriad mechanisms within the TME.

2.4. Factors Contributing to TME Formation. *2.4.1. Inflammation.* Inflammation can destroy thin cell membranes and cause DNA damage, resulting in cellular damage and an abnormal immune response, increasing the risk of tumorigenesis. Indeed, the inflammatory microenvironment and cancer cells exert mutual effects. Inflammatory cells produce various pro-tumor inflammatory mediators, such as reactive oxygen species (ROS), cytokines [e.g., tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6], and growth factors. These inflammatory mediators directly or indirectly contribute to the initiation and progression of tumorigenesis. Moreover, tumor cells enhance the levels of circulating inflammatory

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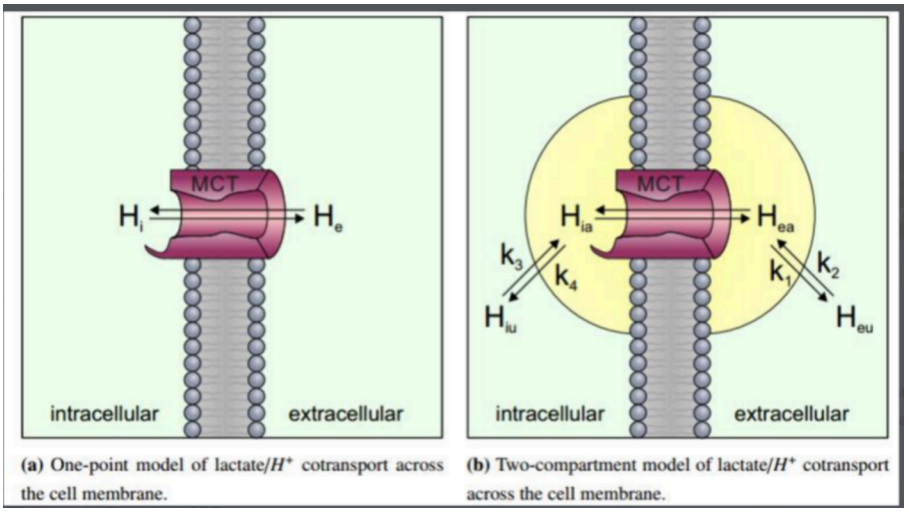

(a) One-point model of lactate/H^+ cotransport across the cell membrane. (b) Two-compartment model of lactate/H^+ cotransport across the cell membrane.

Figure 2. Two models considered in this work illustrate the corresponding proton exchange. Adapted under the CCBY 4.0 DEED license from ref 11. Copyright 2019 the Author(s), licensee AIMS Press.

factors. Chronic inflammation can also lead to chromosomal instability and disordered epigenetic mechanisms involving DNA and histone modification enzymes, microRNAs, and long-noncoding RNAs, leading to tumorigenesis.

2.4.2. Cytokines. Tumors, immune cells, and other cells secrete cytokines. The predominant cytokines associated with tumorigenesis include IL-6, IL-2, interferon (IFN)γ, and transforming growth factor (TGF)-β. These cytokines can accelerate tumor development by mediating complex pathways, including the nuclear factor (NF)-κB, signal transducer and activator of transcription (STAT)3, and other signaling pathways associated with promoting tumor growth, invasion, and metastasis.

IL-6 exists widely in the TME and is key in mediating the relationship between inflammation and tumors. Moreover, IL-6 can promote tumorigenesis by regulating signal transduction pathways such as apoptosis, proliferation, angiogenesis, invasion, and metastasis. Meanwhile, IL-8 enhances the function of lymphocytes and phagocytes by stimulating chemotaxis and granulocyte activation, leading to tumor invasion and migration. In contrast, inhibiting IL-8 expression significantly inhibits colony formation and cell survival *in vitro* and inhibits tumor cell invasion and growth *in vivo*. Aside from its primary neutrophil chemotactic ability, IL-8 promotes neutrophil lysosomal activity and phagocytosis. Upon prolonged inflammation, PCa cells become stimulated; IFN-γ and TNF-α can induce human PCa cell lines to release ILs, resulting in tumor-derived soluble factor, which may contribute to the development of the cancer toward an untreatable phenotype.

2.4.3. Angiogenesis. Tumor cells release angiogenic factors to stimulate angiogenesis, enhancing tumor cells' nutritional supply and diffusion. Angiogenesis is an intricate and multistage process that involves various components, including endothelial cells, the ECM, and soluble factors. PCa cells produce angiogenic factors. The "start switch" of early angiogenesis is associated with the refinement of the intraductal vascular system in prostatic epithelial tumors, as well as the expression of hypoxia-inducible factor (HIF)-1α and vascular endothelial growth factor (VEGF) tyrosine kinase receptor (VEGFR)-1.[8]

2.4.4. Immune System. Immune cells can recognize and destroy tumor cells; however, the host immune cells can also be destroyed by tumor cells or lose their ability to recognize tumors, thus forming a state of immune escape for tumors. The role of immune cell infiltration in cancer treatment has been recognized for over a century, with two key mechanisms proposed to explain the immune cell infiltration in response to cancer. The first suggests that cancer cells are antigenic and can stimulate an active immune response. The second theory proposes that immune surveillance is necessary for cancer development and control. The primary immune cells involved in these processes include lymphocytes and bone marrow cells. In addition to various effector adaptive immune cells, the TME contains T helper (Th)1, Th2, Th17, and regulatory T (Treg) cells. Infiltrating lymphoid cells, dendritic cells, and follicular helper cells have been associated with favorable prognostic effects. Conversely, M2 macrophages and polymorphonuclear cells are considered to be unfavorable cell types in the TME.[9]

2.4.5. Acid–Base Balance. The acid–base balance is another important factor in establishing the TME and is regulated by the synergistic interaction between various membrane transporters and carbonic anhydrase (CA). Na +/H+ exchanger 1 (NHE1) is the primary pH regulator, and its activity increases during the initial stages of tumor formation. Activation of NHE1 by oncogenes leads to intracellular alkalization and extracellular acidification (Figure 2). Experimental and mathematical models of *Xenopus* oocytes have shown that effective lactic acid shuttling through monocarboxylic acid transporters requires CA on both sides of the plasma membrane.[10,11] The changes in tumor metabolism and regulation of the intracellular acid or base state reverse the pH gradient in solid tumors, which is recognized as a shared characteristic that can elicit various physiological responses, including heightened glycolytic activity, augmented cell proliferation, apoptosis suppression, immune system evasion, and enhanced cell migration. Therefore, regulating pH in tumor cells involves the coordinated interplay between acid or base transporters, forming physical and functional complexes with CA. This interconnection is referred to as "transport metabolism." These protein complexes usually exist in the migrating cells and have important roles in tumor pH regulation and cell migration.[12]

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2.4.6. Gene Mutation. One of the primary causes of tumorigenesis is gene mutation, endowing tumor cells with a certain fitness advantage that contributes to TME formation. These factors are often interrelated and jointly affect TME formation and development. Genetic mutations can arise spontaneously or can be triggered by external factors. Although not all mutations result in substantial alterations in cellular function, mutations in genes with critical functions can give rise to reproductive disorders. Mutation is the primary method to transform proto-oncogenes into carcinogenic states. The gradual accumulation of sudden life changes can lead to cancer. Somatic mutations may impact internal DNA replication mechanisms, defective DNA repair, enzymatic modification of DNA, or a combination of these effects.

Cancer cells also exhibit altered DNA methylation patterns along with mutations in gene sequences compared with normal cells. During carcinogenesis, DNA hypomethylation contributes to various molecular events, such as microsatellite instability and transcriptional activation. Methyl CpG, a region closely associated with cancer etiology, accounts for approximately 37% of somatic p53 mutations. Different mutation processes vary among tumor types and cancers.[13] Some somatic mutations result from skin exposure to ultraviolet radiation, lung smoke exposure, or abnormal DNA maintenance. Accordingly, an increased research focus has been directed toward studying genetic mutations to identify new molecular mechanisms and treatment targets to benefit patients with cancer.

2.5. Definition and Composition of the PCa Microenvironment. Extensive research has been conducted on the genomic, epigenetic, and metabolic factors contributing to PCa development in epithelial cells. However, cancer cells continuously interact with the TME, which can influence cancer cell development, progression, and degeneration. During the process of carcinogenesis, cancer cells can deliver soluble factors and vesicles that engage in paracrine signaling and promote tumor metastasis. The surrounding plays a crucial role in tumor development by providing nutrients and growth factors that facilitate cell proliferation. Moreover, noncancerous stromal cells contribute to the formation of the TME, supporting the replication and growth of cancer cells, ultimately fostering tumor progression. The TME in prostate adenocarcinoma is a particularly complex entity.

2.5.1. Cancer Cells. Understanding the full extent of the hierarchical structure of normal prostate epithelial cells is a requisite for identifying and studying the characteristics of PCa-origin cells. Mouse models are most commonly used in *in vivo* cancer research, providing considerable insights into the pedigree relationship, intrapedigree heterogeneity, and pedigree plasticity among cells under stress conditions. These studies conclude that the basal and lumen cells are maintained independently to a large extent under physiological conditions. Under specific pressures or experimental conditions, these cell types have the potential for dual differentiation. However, it remains unclear whether the hierarchical organization of human prostate cells is comparable to that of mice. Experiments by independent research groups have shown that mouse and human cell types can be transformation targets. However, whether diseases from different sources exhibit unique clinical behaviors remains controversial[14,15] and requires further investigation. That is, by elucidating the cells from which PCa originates, new prognostic markers can be identified for the early detection of invasive PCa. This will provide insights regarding the susceptibility of tumors to treatment and could further inform the development of novel therapeutic strategies. Many recent studies have used myriad experimental systems to identify potential cell types of anterior adenocarcinoma, such as tissue recombination methods for studying epithelial−stromal interactions, cell origin analysis of organ-like models, and analysis of genetically engineered mice to study cell origin types by introducing carcinogenic events into different epithelial subsets *in vivo*.[16] The current consensus is that basal and lumen cells appear to represent the origin of PCa, at least in specific experimental paradigms.

2.5.2. Immune Cells. Immune cells, including T lymphocytes, B lymphocytes, monocytes, and macrophages, recognize and attack tumor cells. Among these, T cells, specifically cytotoxic T lymphocytes (CTLs), play the most pivotal role in immune-mediated tumor clearance.[17] Tumor-infiltrating lymphocytes (TILs) are the main mediators of the antitumor immune response and are used to calculate immune scores to quantify the degree of immune infiltration as a predictive classification of solid tumors. PCa is characterized by increased infiltration of CD8+ T cells, which is associated with poor prognosis,[18] However, the underlying mechanism remains unclear. Some studies suggest that high T cell infiltration is related to the codeletion of *BRCA2* and *RB1*, a typical feature of highly invasive PCa with a poor prognosis.[19] The T-cell infiltration region of PCa lymph node metastasis has a dysfunctional signal transduction pattern and high expression of T-cell depletion markers such as PD-1 and TIM-3,[20] B cells are also more abundant in PCa, and their accumulation is associated with more aggressive disease.[21] B cells produce lymphotoxins, activating IKKA−STAT3 and BMI1 signal transduction and accelerating castration resistance, metastasis, and diffusion in PCa.[22] Macrophages can phagocytose and eliminate foreign and harmful substances, including cell fragments and tumor cells. Circulating monocytes differentiate into mature macrophages depending on their internal environment and other conditions. Under certain conditions, macrophages are collected during tumor microring and differentiate into tumor-associated macrophages (TAMs). Macrophages can undergo polarization into two distinct subsets: classically activated macrophages (M1) and alternatively activated macrophages (M2). Within these subsets, M2 macrophages and a few M1 cells are considered TAMs and exhibit a reduced capacity to engulf tumor cells, actively contributing to tumor progression by facilitating tumor cell evasion from immune surveillance and promoting metastasis to distant tissues and organs. M1-type macrophages are characterized by MHC-II, CD80, and CD86 expression on their surface and the production of proinflammatory cytokines, such as IFN-γ, TNF-α, and IL-1. Hence, M1 macrophages predominantly function in eliminating pathogens and tumor cells. In contrast, M2-type macrophages express CD163, CD204, and CD206 on their surface and secrete anti-inflammatory cytokines, including IL-10, Arg-1, and TGF-β. Accordingly, M2 macrophages perform anti-inflammatory and repair functions. High-density M2-type macrophage infiltration in PCa tissue predicts early biochemical recurrence after radical prostatectomy and is associated with castration resistance. In the PCa TME, the antitumor effects of immune cells are often inhibited or maladjusted.[23]

2.5.3. Vascular Endothelial Cells. The vascular network plays an important role in the physiological balance of the prostate and tumor evolution. Tumor-related vessels exhibit

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distinct characteristics from normal vessels, with inconsistent pericyte coverage and abnormal branches. PCa requires a large amount of nutrients and oxygen to maintain growth and metastasis; therefore, the blood vessel density in tumor tissues is often higher than in the normal prostate. Simultaneously, vascular endothelial cells secrete many growth factors, such as VEGF and basic fibroblast growth factor (bFGF), which can stimulate the growth of new blood vessels. Normal tissues and the surrounding PCa tissues show differences in microvessel density, along with variations in VEGF, VEGF-C, and VEGFR-3 expression, suggesting that increased expression of these growth factors is related to the development of PCa. VEGF promotes increased microvessel density in tumor tissue, facilitating cancer cell growth. VEGF-C and VEGFR-3 predominantly promote lymphangiogenesis in the tumor tissue, subsequently promoting cancer cell metastasis.

2.5.4. Fibroblasts. Fibroblasts are a well-characterized group of prostate mesenchymal cells. Under normal physiological conditions, fibroblasts play a crucial role in monitoring the ECM and connective tissue and participate in tissue repair processes. Most prostate fibroblasts originate from the mesoderm, while a smaller proportion arise from the nerve crown. However, in the TME of PCa, the population and viability of fibroblasts become altered. Specifically, cancer-associated fibroblasts (CAFs) emerge as the most significant stromal cells within the solid TME. CAFs can be divided into three subpopulations: myofibroblastic, immune-regulatory CAFs, and antigen-presenting (ap)CAFs. Myofibroblastic CAFs reorganize the ECM, produce hyaluronate, fibronectin, and collagens, and induce morphological alterations and increased stiffness. Immune-regulatory CAFs and apCAFs contribute to cancer inflammation and modulation of immune responses in the TME. CAFs can promote tumor growth through several mechanisms, including (1) direct stimulation by secreting growth factors to proliferate tumor cells; (2) induction of angiogenesis and remodeling of the ECM; and (3) recruitment and functional regulation of immune cells in the TME mediated by the secretion of cytokines and chemokines, thus inducing tumor inflammation. Although segmented, CAFs can induce tumor inflammation; immune cells and CAFs are not the main participants in the tumor immunosuppressive circuit. The cross-talk between CAF and M2 macrophages promotes PCa, and M2 macrophages stimulate CAF development by triggering PCa cell epithelial−mesenchymal transition (EMT) and neovascularization.[24] Furthermore, ADT can induce hypoxia, which triggers the transdifferentiation of CAFs into CXCL13-producing myofibroblasts.[25] This subassembly of CAFs subsequently recruits IgA+ plasma cells, thereby blocking CTL activity.[26] The PCa-associated reactive matrix is characterized by an increased fibroblast/myofibroblast ratio, which increases the expression of pathotoxin, fibrin-specific protein 1, and dehydrogenase.[27]

2.6. Characteristics of the PCa Microenvironment.

2.6.1. Hypoxia. Insufficient angiogenesis and cancer progression often lead to hypoxia in solid tumors, including PCa. In the early stages of PCa development, hypoxia can arise from the accumulation of acidic metabolites or active oxidants. To adapt to this hypoxic environment and regulate the TME, cells accumulate hypoxia-inducible factors (HIFs). Studies have applied a hypoxia therapy strategy combining hypoxia imaging and hypoxia cell targeting in human PCa xenografts under the control of a hypoxia response element. The key steps by which HIF promotes tumorigenesis include angiogenesis, metabolism, proliferation, and metastasis (Figure 3). Growth factor signal pathways may also regulate HIF-1α subunits without

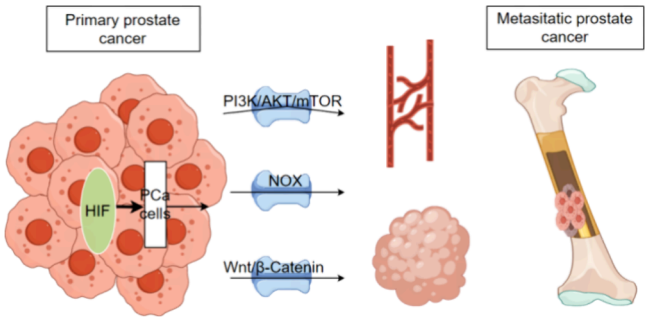

Figure 3. Key steps by which hypoxia-inducible factors promote tumorigenesis include angiogenesis, metabolism, proliferation, and metastasis. Created with figdraw.com. License ID: STYTP3823b.

hypoxia. Additionally, the expression of HIF-1α and hypoxia are closely related to prostate stem cell markers. Stem cell-like cancer cells are increasingly identified as a subpopulation that leads to metastasis and radiotherapy/chemotherapy resistance in PCa. This significant pathway promotes adaptive tumor development and also facilitates the activation of other hypoxia-induced pathways, including the PI3K/AKT/mTOR, NOX, Wnt/β-catenin, and Hedgehog signaling pathways, which collectively contribute to tumor survival and growth. Furthermore, hypoxia promotes the recurrence, metastasis, and EMT of PCa, and enhances the stability, volatility, and transcriptional activity of ARs, ultimately promoting the development of CRPC.[28]

2.6.2. Acidity. The acidity of the PCa microenvironment is characterized by a low pH value in the PCa tissue. This acidic microenvironment is mainly due to the accumulation of acidic metabolites caused by the abnormal metabolism of tumor cells and the lactic acid and bicarbonate ions released by the activities of tumor-related cells and immune cells. The acidogenic metabolism of PCa cells is mainly carried out through glycolysis; under hypoxic conditions, glucose is converted to lactic acid and released into the surrounding tissue. This metabolic mode enables tumor cells to quickly acquire energy and promote their growth and reproduction. Simultaneously, the accumulation of lactic acid leads to a further increase in the acidic environment of PCa cells. Specifically, an acidic microenvironment may influence the biological behavior of PCa by promoting tumor invasion and metastasis and increasing invasiveness to the surrounding tissues and blood vessels. An acidic microenvironment can inhibit the function of immune cells and reduce the recognition and killing of tumor cells, thereby improving the possibility of tumor escape immune monitoring. Acid rings can influence the curative effect of many anticancer drugs and reduce their killing effects on tumor cells. Understanding the acidic characteristics of the anterior adenocarcinoma microenvironment is important for further study of the development of therapeutic strategies for acidic environments. The excessive accumulation of lactic acid in the TME has been proposed as a potential suppressor of anticancer immunity. Recent research supports this hypothesis and sheds light on the mechanisms through which lactic acid, in conjunction with an acidic TME, hampers immune cell functions. Specifically, lactic acid is recognized as a critical immunomodulatory molecule. Lactic

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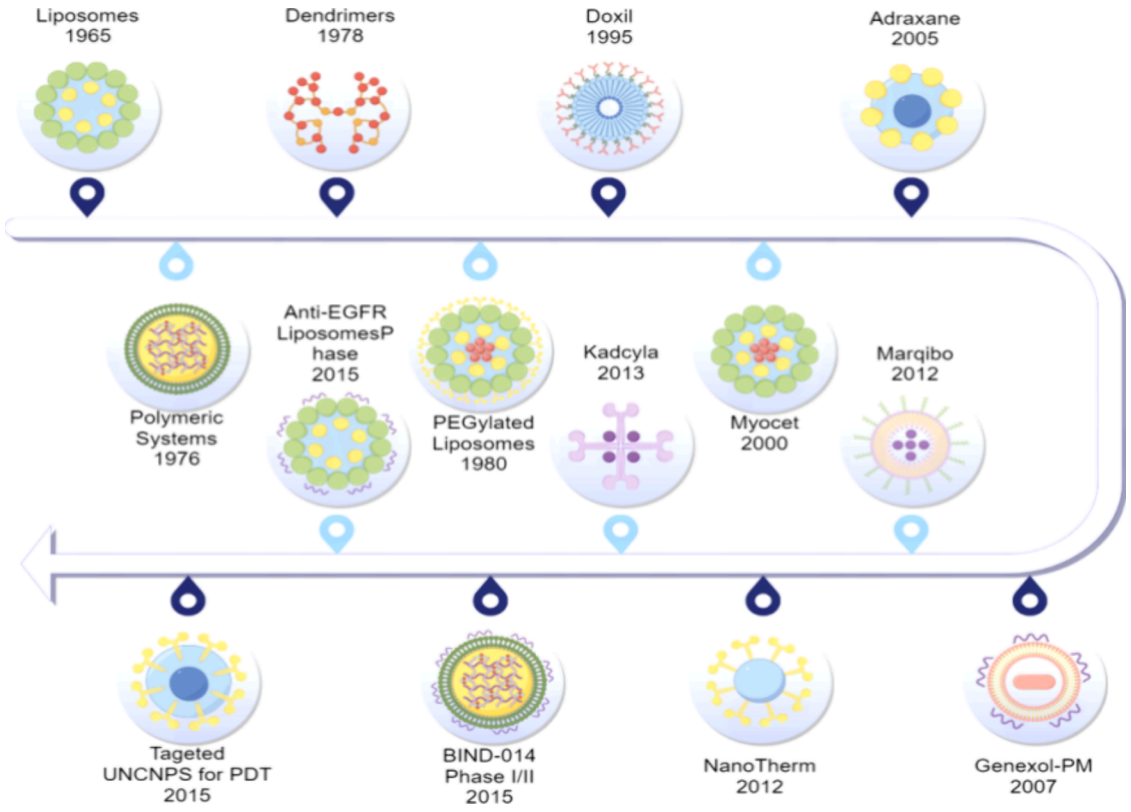

Figure 4. History of nano anticancer drugs. Created with figdraw.com. License ID: IITOW3c6eb.

acid within the TME exerts inhibitory effects on antitumor immune responses by negatively modulating the function of tumor-infiltrating immune cells.[29] First, lactic acid impairs the differentiation of monocytes into dendritic cells, consequently reducing their ability to effectively present antigens. Second, lactic acid inhibits the antitumor activity of immune effector cells. Third, it promotes the infiltration of immunosuppressive cells. These immunosuppressive cells collectively contribute to inhibiting antitumor immune responses, facilitating immune evasion by cancer cells. An acidic TME and elevated lactic acid levels also significantly affect macrophages.[30] Activation of macrophages *in vitro* under acidic pH fragments with physiological pH 7.2 or lower than 7.0 was associated with increased expression of CD206. When the acidic pH returned to a neutral pH, the expression level of CD206 in TAMs decreased significantly.

2.6.3. Oxidative Stress. Oxidative stress activates various transcription factors such as NF-κB and AP1. The maladjustment between oxidative and antioxidant substances in the body has been implicated in initiating and developing tumorigenesis, particularly in PCa. Abnormal changes in prostate cancer and ROS levels become increasingly common with age, and ROS signal transduction plays a significant role in the development of malignant tumors. Oxidative stress is associated with various pathological conditions, such as inflammation and infection, that contribute to this process. ROS, as byproducts of normal cellular metabolism, can activate signaling pathways in response to intracellular and extracellular environmental alterations. Over time, a chronic increase in ROS induces somatic mutations and tumor transformation. Consequently, for patients with early PCa, physical activity can slow the progression of PCa, with ∼40% of related studies showing that superficial exercise has a protective effect on the risk of PCa.

2.6.4. Immunosuppression and Immune Escape. During the growth of cancer cells, insufficient hemoperfusion in the vascular system leads to an anoxic environment. HIF-1α is activated in response to this change, triggering signaling in vascular endothelial cells, leading to increased transcription of *VEGF*, consequently initiating tumor angiogenesis.[31] Immunosuppression within the TME is predominantly mediated by Tregs, characterized by the expression of CD4, CD25, and FoxP3 surface markers. These Tregs and other suppressor cell types are considered the primary agents contributing to tumor immune evasion and pose a significant obstacle to tumor immunotherapy.[32] Tumor-derived Tregs have been discovered to exhibit higher inhibitory activity than naturally occurring Tregs.[33] Tregs are recruited to the TME through the production of chemokines, which are primarily mediated by tumor cells. Additionally, evidence shows that TGF-β can promote the local transformation of CD4+ T cells into inhibitory Tregs.[34] Another basic mechanism of tumor evasion from immune surveillance involves downregulating the major histocompatibility complex I pathway, proteasome subunits of latent membrane protein, antigen-processing-related transporters, and tapasin.[35] Therefore, the downregulation of tumor antigen expression leads to increased tumor occurrence and metastasis because CTLs cannot recognize target antigens on cancer cells.[36] Tumors can weaken the function of CTLs by producing a variety of immunosuppressive cytokines in cancer or noncancer cells in the TME (specifically immune and epithelial cells), thus evading immune surveillance. TGF-β is the main immunosuppressive cytokine.[37] Additionally, TNF-α, colony-stimulating factor-1, and type I IFN can promote tumor growth.[38]

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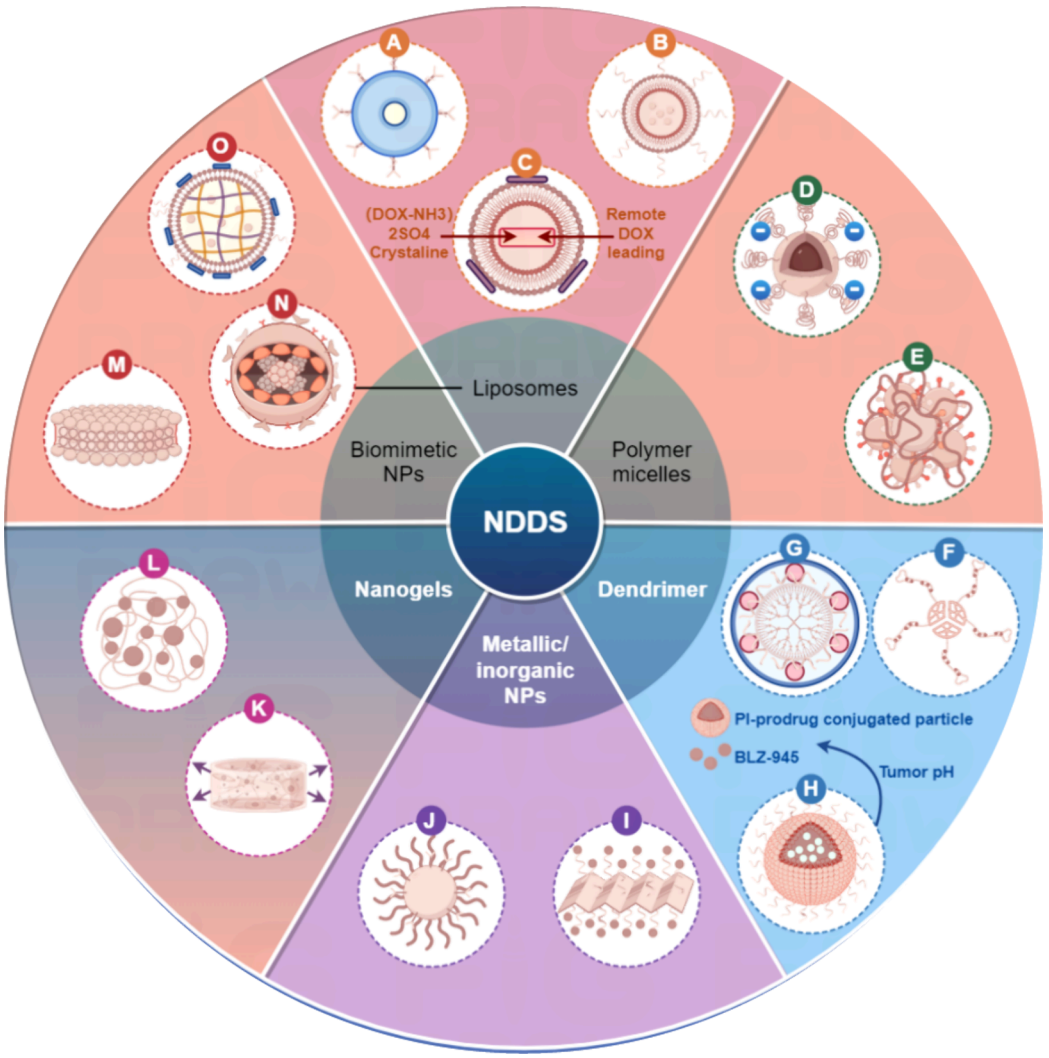

Figure 5. Classification of nanodelivery systems. A-C: Liposomes are spherical vesicles composed of one or more phospholipid bilayers, similar to the structure of cell membranes. These vesicles contain a water core and two parts: the hydrophilic polar head, which can be charged with positive or negative ions; and the hydrophobic hydrocarbon chain, which varies in length and unsaturation. D-E: Polymeric micelles are core−shell type nanoparticles formed by the self-assembly of amphiphilic block copolymers in selective solvents. Typical polymeric micelles have a spherical shape and their size ranges from 10 to 100 nm. F-H: Dendrimer is a polymer with nanoscale size, multifunctional surface, high branch and cavity internal structure, synthesized by step-by-step iterative addition of monomers from a multifunctional core, which can achieve high polymerization rate, surface group modification and high molecular weight synthesis. It can be used to label radionuclides to enhance the imaging of specific diseased tissues, or combined with gold nanoions to form nanoprobes for targeted CT/MR imaging of tumors. I-J: Metal nanoparticles (NPs) have high stability, reactivity, photothermal and plasmonic properties, and are used as therapeutic agents. K-L: Nanogels, a type of hydrogel with a diameter less than 200 nm and having a three-dimensional reticular structure that is insoluble in water and does not melt. M-O: Biomimetic nanoparticles (NPs) are a nanotechnology that mimics the functions of proteins in nature, replicating their characteristics and functions at the nanoscale to achieve specific biomedical applications. Created with figdraw.com. License ID: WWAWUad4aa.

3. OVERVIEW OF NANOTHERAPY

3.1. Definition and Background of Nanotherapy. Nanotherapy has been used to treat tumors, cardiovascular diseases, and nervous system diseases. This system involves administering NPs or small molecules to deliver drugs directly to the lesion location, improving therapeutic effectiveness. Nanotechnology can be applied to create NPs with specific functions, such as enhanced drug-targeting ability, increased solubility, and prolonged drug half-life, to improve therapeutic efficacy.

Researchers have gradually demonstrated the myriad unique characteristics of NPs and small molecules. Nanotechnology has contributed to the early detection of cancer diagnosis and has helped reduce patient mortality. When the NPs are distributed at appropriate intervals to facilitate their accumulation at the tumor site, the targeted drugs can reduce toxicity. Nanotype drugs include various carrier molecules, exhibit therapeutic effects, and can be altered by chemical and physical changes according to the optimal properties of patients.[39]

3.2. History of Nanotherapy. Nanotherapy was first developed in the early 1990s. In 1995, Professor Samir Mitragotri, a pharmaceutical chemist, demonstrated the first application of NPs to successfully deliver drugs to the liver. In 1997, Professor Alexander Florence, a pharmacologist at Niujin University in the United Kingdom, used lipid NPs to deliver chemotherapeutic drugs to liver cancer cells. This study is considered a milestone in nanotherapy. In 2001, the American Institute of Nanotechnology Industry (NanoTech Institute)

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was established, providing important support for the progress of nanotechnology and the application of nanotherapy. In 2005, Abraxane was the first drug prepared using nanotechnology to treat breast and lung cancers, marking the formal entry of nanotherapy into the clinical stage (Figure 4). Various nanomaterials have emerged in recent years with further developments in nanotechnology, such as thermosensitive, metal-based, and nucleic acid NPs. The application of these new NPs has further promoted the development of nanotherapy.

3.3. Nanotherapy Classification. Nanoparticles are classified based on their structure and materials, including magnetic NPs, metal NPs, nanocrystals, nanoporous materials, organic and inorganic nanomaterials, and organic−inorganic composites (Figure 5).

3.3.1. Magnetic NPs. Medical magnetic NPs are a class of superparamagnetic nanomaterials that can accumulate in tumor tissues through the bloodstream. By utilizing magnetic particle imaging technology, visualizing and quantifying the concentration of these magnetic particles within the living body is possible. This imaging technique facilitates tumor imaging, allowing for improved detection and characterization of tumors. The nonlinear magnetization response characteristics of magnetic particles and the spectral characteristics of magnetic particle signals under an alternating field were studied through modeling and simulation analyses, as well as the relationship between harmonics and the sample size of the medical magnetic NPs. On this basis, an experimental signal detection system was built, the spectral characteristics and power spectral density of the detected signal were analyzed, and the relationship between the signal and excitation frequency was studied. By exploiting magnetic NPs' characteristics under a magnetic field, they can be localized to specific parts or fine cells to achieve their therapeutic goal.

3.3.2. Metal NPs. Metal NPs use the sensitivity of metals to light, heat, magnetism, and other energies to achieve therapeutic results such as inhibiting cancer cell growth at high temperatures.

3.3.2.1. Silver NPs (AgNPs). Silver and its compounds have been used for millennia for their antibacterial and therapeutic properties. Historical records indicate that Hippocrates employed silver preparations to cure ulcers and accelerate wound healing. In 1852, Sims successfully used a fine silver thread to suture a vesicovaginal fistula resulting from childbirth, greatly reducing the risk of infection. Nonetheless, with the advent of antibiotics in the 1940s, the medical use of silver diminished. However, since the 1980s, the misuse of antibiotics has led to global concerns over bacterial drug resistance. Consequently, silver has regained attention, particularly in conjunction with advancements in nanotechnology seen in the early 21st century. AgNPs are considered to have high antibacterial activity, with the ability to kill various pathogens, including deworming ability to effectively kill nematodes. The antibacterial mechanism of AgNPs mainly involves the destruction of the bacterial cell wall, producing ROS, and destroying the DNA structure. AgNPs can also be used to effectively treat various cancers, including cervical cancer, breast cancer, hepatocarcinoma, glioblastoma, and PCa. Moreover, the anticancer activity of AgNPs is related to their physical and chemical properties in various tumor cells. Studies have shown that smaller AgNPs may cause increased phagocytosis and induce better anticancer activity. Orbicular AgNPs showed better cytotoxicity because of their higher surface-area-to-volume ratio.[40] AgNPs exhibit broad-spectrum anticancer activity through a variety of mechanisms. Extensive experiments have demonstrated the capability of AgNPs to inhibit the propagation and survival of tumor cells. The mechanisms underlying this effect involve disruption of the cancer cell ultrastructure, followed by induction of ROS production and DNA damage, ultimately leading to apoptosis or necrosis.[41,42] AgNPs can enhance apoptosis by modulating p53 expression[43] and regulating the important HIF signaling pathway.[44] Additionally, AgNPs can shut down the cell cycle in cancer cells.[45,46] Furthermore, treatment with AgNPs can cause sub-G1 phase arrest and subsequent apoptosis in certain cancer cells.

3.3.2.2. Gold NPs (AuNPs). The optical properties of AuNPs make them particularly suitable for hypersensitive testing and imaging-based treatment techniques for fatal diseases such as cancer. In cancer medicine, a range of AuNPs have emerged as valuable tools,[47] offering promising applications in cancer therapeutic interventions. The optical properties of AuNPs are determined by surface plasmon resonance, which involves the resonance of gold electrons to induce an incident radiation reaction, enabling the absorption and scattering of light. This unique property of AuNPs establishes them as a potential platform for advancing cancer therapy. Some AuNPs with specialized shapes make the photon capture cross-section five times larger than photothermal dyes. These properties are used to obtain local heat for destroying cells or releasing drugs, which is the basis of therapeutic applications. Moreover, AuNPs have adjustable properties to fabricate specific NPs, leading to the transfer of plasmon resonance from 520 to 800−1200 nm.[48] The shape of NPs from 15−30 nm nanospheres to 3.5−5.5 nm aspect ratio nanorods can cause changes to their optical properties.[49] Thus, AuNPs can be used for deep-tissue treatment using photothermic and photoimaging methods.[50]

Traditional drug delivery routes, such as oral or intravenous administration, cause the drug to spread throughout the body; however, only a small part of the drug ultimately reaches the lesion to exert its therapeutic effects. NPs have an advantage in drug delivery. In particular, AuNPs have been used as drug carriers owing to their surface plasmon resonance, optical, and tunable properties. They can also be prepared in various nuclear sizes (1−150 nm), facilitating the management of their dispersion. The surface of AuNPs is negatively charged, simplifying their modification. Therefore, their function can be enhanced by binding to various biomolecules. Methotrexate (MTX) has been used to treat cancers for many years. Compared with free MTX, methotrexate showed higher cytotoxicity in cancer cells when combined with AuNPs.[51] In addition, doxorubicin (DOX) showed enhanced toxicity in multidrug-resistant MCF-7/ADR breast cancer cell lines when binding to AuNPs through acid-unstable connectors, thus overcoming multidrug resistance to some extent. AuNPs bind to the absorbed drug and then respond to its release into the cell.[52] The use of peptide drug conjugates as anticancer agents has been studied. When combined with AuNPs, the half-life of the peptide drug conjugates was significantly increased, and the cytotoxicity was not reduced. In addition to synthetic drugs, plant-derived compounds demonstrate potential as anticancer agents. For instance, when combined with AuNPs, kaempferol exhibits enhanced apoptosis inhibition in MCF-7 breast cancer cells. Combining botanical substances with AuNPs offers a promising strategy for treating cancer.[53]

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Moreover, AuNPs play roles in photothermal therapy (PTT) and photoimaging. Studies have found that AuNPs with a maximum absorption wavelength of 795 nm and branched-chain gold nanoparticles incorporated with nanoantibodies have effective activity against tumor cells without harming normal cells using PTT.[54] Lin et al.[55] demonstrated the application of AuNPs in PTT for the first time using 30 nm AuNPs conjugated with IgG antibodies. During photodynamic therapy (PDT), photosensitizers such as porphyrin are administered intravenously and activated by specific wavelengths of light. This process leads to energy transfer, generation of ROS, and subsequent cell apoptosis. Recent studies have utilized both PTT and PDT for melanoma xenotransplantation in mice. The main drawback of PDT is that the photosensitizers are often insoluble in the *in vivo* microenvironment, limiting their absorption by tumor cells. However, several studies have demonstrated that photosensitizers can bind to AuNPs, enhancing their uptake ratio and facilitating targeted delivery to cancerous tissues. PDT offers several advantages, including minimal invasiveness, noncumulative toxicity, and demonstrated efficacy in treating various types of cancer, such as lung and skin cancer. This treatment approach has shown promise in reducing adverse events and is considered an effective therapeutic modality.[56]

3.3.3. Nanocrystals. Nanocrystals typically comprise single or polycrystalline nanocrystals with a relatively high specific surface area, fine size, and unique physical, chemical, and electrical properties. Raw chitin polymers have gained significant popularity in recent years as a green technology across various industries. Nanotechnology has enabled the production of chitin nanocrystals (ChiNCs), which are nanoscale rod-shaped natural materials. ChiNCs possess unique characteristics, including biodegradability, biocompatibility, renewability, a rod-like structure, excellent surface and interface properties, and physicochemical and thermomechanical properties. These attributes make ChiNCs an appealing and environmentally friendly product with diverse applications, particularly in the medical and pharmaceutical sectors.[57] Cellulose nanocrystals (CNCs) are tiny, rod-like particles derived from cellulose, a natural polymer in plant cell walls. CNCs are typically obtained through the controlled acid hydrolysis of cellulose fibers. CNCs have gained significant attention in various fields due to their unique properties and potential applications. Furthermore, CNCs have a unique ability to interact with water and form stable suspensions. This property enables their usage in drug delivery systems. Their versatility and favorable properties make CNCs a promising choice in biomedicine.[58] Lanthanide-doped nanocrystals exhibit unique optical properties, including narrow emission bands, long emission lifetimes, and resistance to photobleaching. These properties make them suitable for applications in biological imaging, such as fluorescence imaging, bioimaging, and molecular imaging. By incorporating lanthanide-doped nanocrystals into contrast agents, researchers can improve the sensitivity and resolution of imaging techniques such as magnetic resonance imaging (MRI) and optical imaging.[59] Lanthanide-doped nanocrystals can also be used for therapeutic purposes. Nanocrystals can be employed in PDT and PTT by utilizing their optical properties. In PDT, lanthanide-doped nanocrystals generate ROS upon light activation, which can selectively kill cancer cells. In PTT, the nanocrystals convert absorbed light into heat, leading to localized hyperthermia and targeted destruction of cancer cells. Additionally, lanthanide ions themselves have shown potential in drug delivery systems, where they can act as carriers for therapeutic agents.

3.3.4. Nanoporous Materials. Nanoporous materials are used as carriers to transport drugs to targeted tissues or specific cells, which have the advantages of high efficiency and low toxicity. Porous nanomaterials have great advantages over nonporous nanomaterials because of their large surface area, large pore volume, low mass density, and tunable size.[60] Nanoporous materials provide a suitable environment for tissue regeneration and engineering. Their porous structure can mimic the ECM and facilitate cell adhesion, proliferation, and differentiation. These materials can act as scaffolds for new tissue growth, promoting wound healing and tissue regeneration. Additionally, nanoporous materials can be functionalized with bioactive molecules or growth factors to further enhance tissue integration and regeneration. Moreover, nanoporous materials offer a solution in cancer treatment by utilizing their porous channels to capture and transport insoluble drugs. Their high surface area enables efficient drug adsorption, potentially reducing drug administration dosage in patients.[61] The surface of NPs can be modified by incorporating various stimuli-responsive elements, allowing for controlled drug release. Research on aerosolization and drug delivery of NPs has been ongoing since 1990, with particle size, shape, and porosity affecting the deposition dynamics in the lungs.[62,63] In contrast to nonporous materials, nanoporous materials offer adjustable pore sizes, higher sedimentation potential, improved lung dispersion, and enhanced physical and chemical stabilities.[64,65] Many nanoporous materials such as mesoporous silica and biodegradable polymers exhibit excellent biocompatibility and can be tailored to exhibit bioactive properties. These materials can support cell growth, minimize adverse reactions, and promote tissue integration. This makes them suitable for various biomedical applications, including implants, coatings, and drug delivery systems. The possibility of creating core−shell structures and incorporating two different-sized pores in the same material further enhances the versatility of nanoporous materials compared to nonporous alternatives. The release curve of porous materials can also be adjusted based on predictability and repeatability to allow for controlled drug release. For example, after drug injection, the release characteristics of the drug can be better controlled by gradually dissolving the drug or only when receiving a specific stimulus, ultimately blocking the pores. In summary, nanoporous materials offer advantages in drug delivery, tissue engineering, biosensing and diagnostics, imaging, and biocompatibility. Their unique structure and properties make nanoporous materials versatile tools for advancing medical research and improving patient care in various applications.[66] These materials can be classified into three categories based on their pore size: micropores, mesopores, and macropores.[67,68] Both microporous and mesoporous materials can be used as carriers for anticancer drugs. These materials have a high surface area and well-defined pore structures, which allow for efficient loading and controlled release of therapeutic agents. By encapsulating chemotherapeutic drugs within the pores, these materials can protect the drugs from degradation, improve their solubility, and enhance their targeted delivery to tumor sites. This targeted drug delivery minimizes systemic toxicity and improves the therapeutic efficacy against cancer cells.[69,70] Materials with larger mesopores and macropores can effectively adsorb and deliver proteins, peptides, genes, or

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vaccines. These findings highlight the potential of porous materials in drug delivery applications.

3.3.5. Organic Nanomaterials. Organic nanomaterials are composed of organic molecules that contain carbon. Moreover, they are more commonly used than inorganic NPs in drug delivery applications because of their high biocompatibility, low cost, low cytotoxicity, and low immunogenicity.

3.3.5.1. Carbon Quantum Dots (CQDs). CQDs have become the preferred choice for biomedical applications, including drug delivery, therapeutic gene delivery, photosensitizers, and nanocarriers for antibacterial molecules. Furthermore, CQDs have demonstrated great potential in multifunctional diagnostic platforms, biological imaging of cells and bacteria, and the development of theranostic nanomedicines.[71] CQDs have a core−shell structure, where the carbon core is surrounded by a shell of functional groups, such as hydroxyl (−OH), carboxyl (−COOH), amino (−NH2), or other organic moieties. These functional groups can be introduced during the synthesis process or through subsequent surface modifications to tailor the properties and applications of CQDs. The exact composition and structure of CQDs can vary depending on the synthesis method and specific functionalization. However, in general, CQDs are composed of sp2-hybridized carbon atoms, forming a graphene-like structure with a size typically less than 10 nm. The composition and structure of the carbon dots determine their properties. Most carboxyl groups on the surfaces of CQDs exhibit good water solubility and biocompatibility.[72] The surface functional groups and size-dependent properties of CQDs make them versatile nanomaterials with potential applications in various fields, including bioimaging, sensing, energy conversion, and catalysis.

3.3.5.2. Liposomes. Liposomes or lipid NPs encapsulate concentric bilipid cycles formed by organic NPs. Liposomes are composed of molecules such as phosphocholine and cholesterol, water nuclei, and lipid membranes, can transport both hydrophobic and hydrophilic drugs. Over recent years, liposomes have undergone various modifications and have been tested in numerous clinical trials, including their use in lung cancer treatment. Liposomes are excellent vehicles for delivering anticancer drugs. They consist of a lipid bilayer structure that can encapsulate hydrophilic drugs within the inner aqueous core and incorporate hydrophobic drugs within the lipid bilayer. This dual-loading capability allows liposomes to carry a wide range of chemotherapeutic agents efficiently, improving drug solubility, stability, and delivery to tumor sites. Liposomes can also be modified with ligands or antibodies on their surface to enhance targeted drug delivery, specifically to cancer cells, while minimizing damage to healthy tissues.[73] As organic NPs, hybrid liposome conjugates play a critical role in the development and applications porous materials. The United States Food and Drug Administration (FDA) has approved second-generation DOX liposomes for treating various cancers.[74]

3.3.5.3. Synthetic Polymers. Synthetic polymers such as polyvinyl acid (PVA), a copolymer consisting of lactic acid and glycolic acid, have various specific roles in the medical field; they are used as biodegradable materials for tissue engineering scaffolds, drug delivery systems, and surgical sutures. PVA is commonly used in ophthalmic applications, including contact lenses, artificial tears, and ocular drug delivery. PVA is also utilized in wound dressings owing to its moisture-retaining and biocompatible properties. Additionally, PVA-based hydrogels are used in biomedical applications because of their high water content and tissue-like properties, making them suitable for drug release, wound healing, and tissue regeneration. This polymer has received approval from regulatory bodies such as the FDA and the European Drug Administration.[75] Compared to nonporous polymer NPs, porous poly(lactic-*co*-glycolic acid) (PLGA) offers the simultaneous loading of hydrophilic and hydrophobic drugs. PLGA has shown a promising effect in the treatment of lung cancer, exhibiting a high uptake rate, as well as in the treatment of PCa after fixation.[76,77] Some researchers immobilized modified PLGA particles of two drugs (DOX and MTX) at a ratio of 5:1, suggesting that the binding of this dual chemotherapeutic drug to targeted ligands is a promising domain for future lung cancer research.[78] Another needle-to-needle prescription was reported, in which PLGA NPs modified with polyethyleneamine/MIR-34A (p53-regulated microspheres) were treated with microRNA. The degree of cell migration inhibition in cells treated with PLGA NPs was higher than that in cells treated with DOX via direct administration.[79]

3.3.5.4. Porous Biological Particles. Porous biological particles made from natural polymers are formed through the self-assembly of excited molecules combining with organic or inorganic NPs, resulting in diverse structures. These naturally derived protein complexes obtained from biological sources can potentially reduce antibiotic side effects.[80,81] Natural polymers are large molecular compounds extracted from living organisms or natural sources. They comprise different biological molecules such as proteins, polysaccharides, and nucleic acids. Natural polymers can serve as drug delivery systems to efficiently transport anticancer drugs to tumor sites. These polymers exhibit good biocompatibility and biodegradability, gradually degrading and releasing drugs in the body. Polysaccharides such as chitosan, alginate, and gelatin have excellent drug encapsulation and controlled-release capabilities, improving drug stability and targeted delivery. Chitosan, a cationic aminoglycan derived from the partial deacetylation of chitin, is the most extensively studied natural polymer in lung cancer research. Chitosan-based microspheres are employed for injecting various vaccines and can even serve as a method for drug delivery through inhalation.[82,83] From a pharmacological perspective, chitosan microspheres are superior to nonferritin microspheres. However, in this case, the stability of the biological particles may be lost during spraying. Chitosan exhibits polycationic properties; it can interact electrostatically with nucleic acids and nuclear membranes because they are negatively charged, resulting in nucleic acid condensation, protection, and complex uptake. In addition, the amino group of chitosan promotes endosomal escape from the complex.

3.3.6. Inorganic Nanomaterials. Inorganic nanomaterials refer to nanoscale materials composed of inorganic elements or compounds. These materials, which range in size from 1 to 100 nm, exhibit unique photoelectrochemical properties and efficient chemical reaction flexibility. Due to their small size and high surface-to-volume ratio, they possess unique physical, chemical, and optical properties. In recent years, inorganic nanomaterials have gained significant attention for their potential clinical applications.

3.3.6.1. Mesoporous Silica NPs (MSNs). The most common inorganic NPs are based on monodispersed silica, which have a customized uniform mesoporous structure, high specific surface area and pore capacity, selective surface function, enable morphology control, and show good biocompatibility as

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well as biodegradability. The mesoporous structure of monodispersed silica allows small interfering RNA (siRNA) to be transmitted along with other biomolecules, thus effectively transmitting it to the target tissue and enhancing gene expression.[84] Mora-Raimundo et al. proposed a modified MSN system to transport and transmit the SOST gene encoding sclerosin through siRNA and osteostatin through subcutaneous injection.[85]

3.3.6.2. Inorganic Polyphosphate (PolyP) NPs. PolyP is a linear polymer consisting of a chain of phosphate residues, linked by high-energy phospho-anhydride bonds. PolyP is a naturally occurring polymer found in various living organisms, including bacteria, fungi, protozoa, and plants, which can exist in the form of soluble NPs or condensed layers in physiology and synthesis, according to external conditions. In recent years, interest in these polymers has grown owing to their unique morphogenesis and metabolic energy transfer properties. PolyP stands out among other physiological molecules because of its abundance of metabolically available high-energy bonds. This characteristic makes PolyP a critical component in advanced hydrogel scaffolds with significant medical implications. In particular, these hydrogel scaffolds have the potential to be utilized in ATP-dependent tissue regeneration and repair, offering promising prospects in the field.[86] Materials based on a PolyP condensation layer or materials containing soluble PolyP or stable PolyP NPs have also been used for wound healing; the NPs are converted into bioactive PolyP-condensed layers when they contact protein body fluids. PolyP condensation can be utilized to develop anticoagulant therapies. PolyP molecules have been shown to promote blood clotting, and the formation of unwanted blood clots can be prevented or reduced by inhibiting or reducing the activity of PolyP through condensation.[87] PolyP has also been implicated in the activation of inflammatory responses. The inflammatory response can be suppressed by inhibiting PolyP activity through condensation, potentially providing therapeutic benefits for inflammatory conditions. PolyP molecules further play a role in tumor growth and angiogenesis. By targeting and inhibiting PolyP activity, the growth and spread of cancer cells can be hindered, potentially leading to improved cancer therapies. PolyP molecules are involved in the formation and stability of bacterial biofilms, which can contribute to antibiotic resistance. By inhibiting PolyP activity through condensation, the formation and persistence of biofilms can be disrupted, potentially enhancing the effectiveness of antibiotic treatments. Wound healing is a complex process that heavily relies on energy supply. Many factors can lead to a comprised healing function, resulting in nonhealing chronic wounds resistant to conventional treatments. Energy is essential for various aspects of wound healing. Platelets are crucial in providing this energy as they release polyphosphate at the injured site upon activation.[88,89] PolyP serves as a source of ATP, which is a vital energy source, through the combined action of intracellular and extracellular enzymes such as alkaline phosphatase and adenylate kinase.[90,91] Importantly, both of these enzymes are present in the wound bed.[92]

3.3.7. Organic−Inorganic Composites. A new type of material has been formed by combining organic and inorganic substances, which have the characteristics of each of these substances and a small superposition effect.

3.3.7.1. Graphene−Silver NP Composites. Graphene is known for its exceptional mechanical, electrical, and thermal properties. It has a large surface area and high conductivity, making it an ideal material for various fields. Moreover, AgNPs possess antimicrobial properties and have been extensively studied for their potential in clinical applications. Graphene modified by AgNPs has great potential for optical, electrical, catalytic, and electrochemical applications.[93−95] The interaction between reduced graphene oxide (rGO) sheets and Ag fractions results in strong bonding, leading to excellent stability and solubility of the prepared rGO−Ag nanocomposites in water. Compared to other tested nanomaterials, rGO−Ag nanocomposites exhibit a more remarkable inhibitory effect on cell growth. Graphene−AgNP composites have shown potential in cancer treatment through their PTT capabilities, enhanced drug delivery, ROS generation, and synergistic effects. These composites can efficiently convert near-infrared light into heat, leading to localized hyperthermia that selectively damages tumor cells. These composites can also carry anticancer drugs, allowing for targeted delivery and controlled release. Furthermore, the composites can induce the generation of ROS such as singlet oxygen and hydroxyl radicals, which cause oxidative stress and DNA damage in tumor cells. Combining graphene and AgNPs in the composites enhances their inherent properties such as antimicrobial and antiangiogenic effects, leading to improved tumor inhibition. However, further research is needed to fully understand and optimize the mechanisms of action of graphene−AgNP composites in tumors and to ensure their safety and efficacy in clinical applications. Experimental findings have indicated that rGO−Ag nanocomposites hold promise as a material for suppressing the viability of ovarian cancer cells.[96] Similarly, studies have demonstrated that the combination of rGO−AgNP nanocomposites and cisplatin can enhance apoptosis and autophagy in human cervical cancer cells by inducing the production of ROS.[97] Other studies have shown that graphene−AgNP composites have therapeutic effects on neuroblastoma. The mechanism involves the reduction of cell vitality, suppression of cell proliferation, decrease in the number of mitochondria, and increase in the expression of apoptosis-promoting genes. This process ultimately results in the accumulation of autophagosomes and autophagy vacuoles.[98] However, it is important to note that the exact mechanisms of action of graphene−AgNP composites in tumors can vary depending on the specific characteristics of the composites and the TME. Therefore, further research is needed to fully understand and optimize the therapeutic mechanisms of these composites for effective cancer treatment.

3.4. Modes of Drug Delivery. *3.4.1. Nanoscale Drug Delivery Systems.* Nanoscale drug delivery systems are a class of drug carriers designed at the nanoscale level for the targeted and controlled release of therapeutic agents. These systems offer several advantages over conventional drug delivery methods, including improved drug stability, enhanced bioavailability, prolonged circulation time, and targeted delivery to specific cells or tissues. Biocompatible nanomaterials have been used as biomarkers, health products, drugs, and drug delivery systems to detect, diagnose, and treat various diseases. Nanoscale systems have been used as carriers for the delivery of nanodrug delivery. Nanoscale drug delivery systems can be categorized into various types, including liposomes, polymeric NPs, micelles, dendrimers, and inorganic NPs. These systems typically comprise biocompatible and biodegradable materials that can encapsulate or conjugate drugs, allowing for their controlled release. The nanoscale size of

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these carriers enables them to bypass biological barriers, penetrate tissues, and accumulate preferentially in diseased sites such as tumors.[99] Nanoscale drug delivery carriers comprise inorganic, organic, or mixed components. Nanocarriers offer several advantages, including the ability to tune their size, shape, surface properties, and versatile functionality, making them effective vehicles for drug delivery in lung cancer.[100,101] Recent research in this field has demonstrated the potential of nanodrugs for cancer treatment. Nanostructures can deliver drugs either passively or through self-delivery. When targeted to a specific site, the drug is released in a controlled manner due to the low drug content within the hydrophobic environment. The drug is directly bound to the nanostructured carrier material in self-delivery, allowing easy release. However, it is crucial to carefully time the release of the drug from the nanocarrier system to ensure optimal biological activity and efficacy, as releasing the drug too quickly may result in reduced effectiveness.[102] The design of these systems can be tailored to achieve specific goals such as sustained release, triggered release in response to stimuli, or targeted delivery to specific cells or tissues. Surface modifications with ligands or antibodies can facilitate targeted delivery and improve therapeutic efficacy while reducing off-target effects. In active targeting, antibodies and peptides bind the drug delivery system to receptors expressed at the target site.[103] Nanoscale drug delivery systems have extensive applications in various diseases, including cancer, cardiovascular diseases, infectious diseases, and neurological disorders. They can improve drug pharmacokinetics and therapeutic index, minimize side effects, and overcome drug resistance.

3.4.2. Gene Nanodelivery System. NPs have recently been used to deliver genes into cells, change gene expression, and achieve the treatment purpose. Nanomaterials have revolutionized nucleic acid delivery, offering a promising solution to overcome existing limitations. Nucleic acid therapies refer to therapeutic approaches that utilize nucleic acids such as DNA or RNA to treat various diseases. These therapies leverage the ability of nucleic acids to modulate gene expression and protein production, offering potential treatments for genetic disorders, cancers, viral infections, and other diseases.[104] In recent years, noncoding RNA-based therapies have emerged as a promising approach for targeted treatments in cancer and other diseases. Antisense oligonucleotides bind to specific RNA sequences and modulate gene expression by promoting RNA degradation or inhibiting translation. They can be used to target disease-causing RNA molecules such as those responsible for certain genetic disorders or viral infections. Hence, promising methods based on nanodelivery/NPs have been developed to use multiple molecules for systemic drug delivery, improve tumor-targeted delivery, and reduce side effects.[105] SiRNAs are promising therapeutic RNA tools that target defective genes by inhibiting mRNA expression and translation. siRNAs are double-stranded RNA molecules that can silence specific genes by targeting and degrading their mRNA transcripts. This approach can be used to suppress the production of disease-causing proteins. However, siRNAs have limitations such as poor intracellular transport, RNase degradation, rapid renal filtration, and toxicity, limiting their therapeutic efficiency. Nanocarriers have been developed to overcome these defects and improve the antitumor activity of siRNAs. Combining siRNAs and anticancer drugs can produce synergistic effects in cancer cells, making them essential gene modification tools in cancer therapy.[106]

3.4.3. Protein Nanodelivery System. A new type of delivery system has been developed based on the combination of proteins and nanotechnology. Proteins can be used as carriers to stably package drugs or genes and have high biocompatibility and biological activity. In the past decade, there has been growing interest in utilizing food proteins as functional biomaterials for the loading and delivery of various physiologically active compounds, including nutrients, health products, and drugs. Proteins offer distinct advantages compared to other platforms for developing nanodelivery systems due to their biocompatibility, amphiphilic nature, and versatility. Protein nanodelivery systems can be engineered to specifically target certain cells, tissues, or organs. This can be achieved by incorporating ligands or antibodies onto the surface of the protein nanocarriers. These targeting ligands can recognize and bind to specific receptors or markers on the surface of target cells, enabling the selective delivery of the therapeutic proteins to the desired locations. After the protein nanodelivery system targets the specific cells or tissues, it needs to be internalized by the cells to release the therapeutic proteins. This can be achieved through various mechanisms such as receptor-mediated endocytosis or passive diffusion. Once inside the cells, the protein nanocarriers can undergo intracellular processing and release the therapeutic proteins into the cytoplasm or specific cellular compartments. The release of therapeutic proteins from protein nanodelivery systems can be controlled to ensure sustained and localized delivery. This can be achieved by incorporating stimuli-responsive elements into the protein nanocarriers. These elements can respond to specific triggers such as pH, temperature, enzymes, or light, and trigger the release of the therapeutic proteins at the desired time and location. Moreover, protein nanodelivery systems can protect and stabilize the therapeutic proteins via their circulation in the body. The protein nanocarriers can shield the therapeutic proteins from degradation by enzymes or the harsh extracellular environment. This protection helps maintain the bioactivity and effectiveness of the therapeutic proteins until they reach the target site.[107] Nanocapsules have attracted particular attention because they offer an effective and promising method for protecting bioactive compounds and delivering them to target physiological sites to control their release and improve their absorption.

3.5. Modes of Treatment. *3.5.1. PTT.* PTT is a noninvasive therapeutic approach that utilizes light-absorbing agents such as AuNPs or carbon-based materials to convert light energy into heat. This localized heat generation can selectively destroy cancer cells or other targeted tissues. NPs absorb light at specific wavelengths to produce local high-temperature thermal effects that kill cancer or other pathological cells. The integration of PTT with immunotherapy has emerged as a promising strategy to address the limitations of monotherapy in eradicating metastatic and recurrent tumors. This combination not only enhances the efficacy of immunotherapy but also harnesses the unique synergistic mechanisms offered by PTT. During PTT, light is applied to the tissue containing the light-absorbing agents, typically in the near-infrared range. The agents absorb the light, leading to a rapid increase in temperature in the surrounding area. This increase in temperature can induce cell death through various mechanisms, including protein denaturation, membrane damage, and the destruction of cellular structures. PTT can be combined with other therapies such as

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chemotherapy or immunotherapy to enhance treatment outcomes through synergistic effects. This interaction between PTT and immunotherapy encompasses several mechanisms, including immune agonists, immune checkpoint blockade, tumor-specific monoclonal antibodies, and others.[108] PTT has attracted attention because of its effective ablation of tumor cells, in which the released immunogenic tumor fragments activate the host's immune response. Combining PTT with immunotherapy strategies can be broadly categorized into four main approaches: (1) using NPs for PTT while simultaneously incorporating specific antigens to trigger an immune response against the tumor; (2) using NPs for PTT along with immune adjuvants to create an *in situ* vaccine effect, stimulating a robust immune response against the tumor; (3) using NPs for PTT while concurrently targeting immune checkpoints or using other immune regulators to overcome immunosuppression within the TME; and (4) utilizing NPs for PTT in combination with chimeric antigen receptor (CAR)-T cell therapy or cytokine therapy, aiming to enhance the overall therapeutic efficacy against tumors.[109]

3.5.2. Immunotherapy. Immunotherapy represents a new type of therapy realized by nanotechnology combined with immunological principles. Host−tumor immune interactions are crucial throughout the progression of tumors, encompassing tumorigenesis, tumor development, and metastasis. Tumors can trigger a specific immune response through the presentation of new antigens. Moreover, immunogenic cell death (ICD) induced by various factors within tumors can stimulate a potent immune response from the host. However, the tolerable immune microenvironment within tumors can suppress the host immune response, hindering tumor eradication and reducing therapy efficacy. Nanotechnology offers a unique approach to address these challenges simultaneously, facilitating effective and targeted delivery of tumor antigens, promoting continuous ICD, and transforming the immunosuppressive "cold" TME.[110] The disadvantages of traditional immunotherapy include limited efficacy, systemic toxicity, lack of tumor specificity, immune evasion, and limited durability. The combination of NPs and immunotherapy provides a feasible method for overcoming these limitations. NPs can be used to deliver anticancer drugs, enhancing the effectiveness of immunotherapy. For example, by loading immune checkpoint inhibitors or immune stimulants onto NPs, targeted drug delivery can be achieved, leading to enhanced activation of immune cells and antitumor effects within the TME.[111] NPs can also serve as carriers for cancer immunotherapy vaccines. By loading tumor-specific antigens or immune stimulants onto NPs, specific immune responses against tumors can be elicited, inhibiting tumor growth and metastasis. Nanovaccines provide a unique platform to deliver personalized new tumor antigens and adjuvants simultaneously and trigger a strong immune response against invasive tumors. The curative effects of standardized cancer treatments such as chemotherapy, phototherapy, and radiotherapy can be enhanced through NP-based approaches.[112] Studies have shown that exocrine-based nanoimmunotherapy targeting TAMs is a promising strategy for treating glioma and standard primary central nervous system tumors. Exosomes have the ability to cross the blood−brain barrier, making them promising candidates for the treatment of neurological disorders. Exosomes can carry therapeutic molecules such as neuroprotective agents or gene therapy vectors to target neurons and glial cells for the treatment of neurodegenerative diseases, stroke, or traumatic brain injury. Exosomes can be engineered to carry therapeutic molecules such as chemotherapy drugs or siRNA to specifically target cancer cells. They can also be used as vehicles to deliver immune-stimulating molecules such as cytokines or checkpoint inhibitors to enhance antitumor immune responses.[113] Studies have shown that nanoimmunotherapy targeting CD40−TRAF6 signal transduction is effective in the treatment of atherosclerosis.[114] With the development of cancer nanomedicines, immunotherapy has rapidly entered the next stages of medical research. The effectiveness of cancer immunotherapy based on nanomedicine and its application is mainly found in the following five aspects: immune checkpoint inhibitors and nanomedicine, CRISPR-Cas NPs in cancer immunotherapy, core−shell NPs combined with cancer immunotherapy, biomimetic NPs for cancer immunotherapy, CAR-T cells, and cancer nanoimmunotherapy.[115]

3.5.3. PDT. PDT uses a combination of laser and nanomaterials to transport NPs and drugs into the tumor cells together, where the NPs produce a photothermal effect under the irradiation of an external laser, thus killing the cancer cells. PDT has the advantage of not seriously damaging the normal tissues of patients. However, the selectivity of PDT is not absolute, and therefore it may incidentally cause damage to normal tissues. Controlled and accurate delivery of a realistic photosensitizer to the tumor site is a major challenge in traditional PDT. Three generations of photosensitizers have been developed to date, among which the tetrapyrrole series is the most widely used in PDT. Multifunctional nanophotosensitizers developed by nanotechnology and nanomedicine approaches have photosensitive properties, accurate drug release ability, effective response to light stimulation, and hypoxia tolerance. Nanophotosensitizers have been designed to enhance PDT efficiency by increasing the ROS yield, which can improve the sensitivity and conversion efficiency of PDT activation, thereby overcoming the challenging hypoxic conditions in the process of deep-tumor PDT.[116] Currently, PDT is a widely utilized treatment for skin cancer and has also shown promise in the treatment of various other cancer types, including bladder cancer. This therapy is especially advantageous for patients at high surgical risk. Thus, PDT represents an innovative technology in the field of uro-oncology.[117]

3.5.4. Chemical Dynamic Therapy (CDT). CDT is an emerging therapeutic approach that utilizes chemical reactions to generate cytotoxic agents or ROS for the targeted destruction of diseased cells. CDT involves the administration of specific chemical agents that can undergo controlled chemical reactions in the presence of specific triggers such as light or enzymes, leading to cell death. CDT has several advantages as a therapeutic strategy. First, it offers high specificity, as the chemical reactions can be triggered in a localized and controlled manner, targeting only the desired cells or tissues; this minimizes damage to healthy cells and reduces side effects. Second, CDT can overcome the drug resistance often encountered with traditional chemotherapy, as the cytotoxic agents are generated *in situ* through chemical reactions rather than relying on cellular uptake or drug metabolism. Additionally, CDT can be combined with other treatment modalities such as photothermal therapy or immunotherapy to achieve synergistic effects and enhance treatment outcomes. In clinical applications, CDT has been investigated for the treatment of various diseases, including cancer and microbial infections. For cancer therapy, CDT has

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Table 1. Functional Characteristics and Advantages of Different Nanotherapies

Specific nanotherapy	Action characteristics	Functional advantage	Illustration
Magnetic nanoparticles	Make use of their role in magnetic field	Accurate positioning	Magnetic particle imaging
Metal nanoparticles	Sensitive to light, heat, magnetism	Unique physical	Gold and silver nanoparticles
Nanocrystal	Using single crystal or polycrystalline	High specific surface area, small in size	Chitin nanocrystals
Nanoporous materials	Using nanoporous materials as carriers	Highly efficient, low toxicity	Porous nanomaterials
Organic nanomaterials	An organic molecule that uses carbon	High biocompatibility, very low immunogenicity	Carbon quantum dots liposome
Inorganic nanomaterials	Inorganic substances with a size of 1−100 nm	Surface chemical properties more suitable for ligand coupling	MSNs and PolyP
Organic−inorganic composite material	Combination of organic and inorganic substances	Superposition effect	GO-AgNP
Nanodrug delivery system	Wraps the drug half in nanoparticles	Good stability, high solubility and bioavailability	Nanometer carrier
Gene nanodelivery system	Nanoparticles are used to deliver genes into cells	Altered gene expression	MicroRNA
Protein nanodelivery system	A new delivery system based on a combination of protein and nanotechnology	High biological activity	Nanocapsule
Photothermal therapy	Absorption of specific wavelengths of light produces a local high temperature effect	Noninvasive, space−time controllability	PTT combined with CAR-T
Immunotherapy	Combined with immunological principles	Strong pertinence and low-toxicity immune	Checkpoint inhibitors
Photodynamic method	Combination of laser and nanomaterials	Minimal side effects	Photosensitizer
Chemical kinetic therapy	Using Fenton or Fenton-like reactions	Tumor selectivity and few side effects	USPION

been explored as an alternative or adjuvant to traditional chemotherapy; it can selectively destroy tumor cells by activating chemical reactions within the TME or by specifically targeting cancer cells using tumor-specific triggers.[118] There are several nanoplatforms available to provide hydrogen peroxide (H_2O_2) for CDT. For example, H_2O_2 NPs are specifically designed to release H_2O_2, which can convert harmless precursor molecules into H_2O_2 through selective chemical reactions or enzymatic catalysis. By combining catalase enzyme with NPs, the NPs can catalyze the generation of H_2O_2, providing the required therapeutic agent. In addition, glucose oxidase is an enzyme that oxidizes glucose to gluconic acid to generate H_2O_2, which can be combined with NPs to form a nanoplatform. When the NPs come into contact with glucose, glucose oxidase catalyzes the production of H_2O_2, enabling localized CDT. To achieve high-performance tumor therapy, ultrasound is introduced, which exerts its effects on cancer cells through acoustic pore action, cavitation, and thermal effects, further enhancing this specific chemically active tumor therapy. A highly effective tumor treatment system was developed using ultrasound irradiation. In addition, superparamagnetic iron oxide nanoparticles is very useful for contrast-enhanced T1 to use weighted MRI for real-time monitoring of cancer treatment.[119]

3.6. Advantages of Nanotherapy in Tumor Therapy. NPs have specific advantages of small size and high surface activity, enabling surface modification, self-loading, functionalization with micelles, and more. Thus, nanotherapy has therapeutic advantages of strong targeting, high drug delivery efficiency, strong tissue and cell penetration, few side effects, and strong adaptability, making it an important development direction in the field of tumor therapy. As one of the rapidly expanding research areas, nanotechnology holds great potential in addressing various biological challenges, including cancer. NP-based therapies have been successfully introduced in clinical practice to treat pain, cancer, and infectious diseases. Chemotherapy is typically associated with limited tumor targeting, side effects, and low solubility, resulting in the inability of drugs to fully reach the tumor. These shortcomings can be overcome by equipping NPs with therapeutic and diagnostic capabilities, leading to the development of new strategies.[120] Overall, nanotherapy offers the potential to improve the effectiveness and safety of tumor therapy by enabling targeted delivery, enhanced drug penetration, controlled release, combination therapy, and imaging capabilities (Table 1). These advantages make it a promising approach in the field of cancer treatment.

4. MECHANISM OF NANOTHERAPY IN REMODELING THE TME

4.1. Tumor Vascular Remodeling and Blood Supply Regulation. NPs directly act on tumor vascular endothelial cells, reduce the support and nourishment of tumor cells, and inhibit formation of the TME. NPs can also inhibit tumor angiogenesis by releasing specific drugs or RNA molecules to inhibit key molecules in the TME. NPs can specifically target abnormally expressed proteins through RNA interference to reduce their levels, inhibit tumor angiogenesis, and regulate the blood supply.

4.2. Tumor Immune Escape and Immune Regulation. Neutrophils are the most abundant white blood cells in the human blood and are important immune cells against microbial infections. Identifying neutrophils as either promoters or inhibitors of cancer progression has led to categorizing tumor-associated neutrophils (TANs) into antitumor N1 and tumor-promoting N2 subsets. N1-type TANs are typically in a nonactivated state and exhibit antitumor activity. They can produce high levels of ROS and release antitumor cytokines such as TNF-α and IFN-γ to promote antitumor immune responses. N1-type TANs also display antiangiogenic capabilities by inhibiting the production of VEGF and other molecules involved in tumor angiogenesis. N2-type TANs are in an activated state and exhibit immunosuppressive and pro-tumor activities. The main characteristic of N2-type TANs is the production of a large amount of anti-inflammatory cytokines such as IL-10 and TGF-β, as well as pro-inflammatory cytokines such as IL-23. These factors can suppress immune cell activity and promote

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tumor cell proliferation and metastasis. Additionally, N2-type TANs can support tumor angiogenesis by producing molecules such as VEGF to facilitate the formation of new blood vessels. Moreover, the subset composition of TANs is dynamically regulated and can transition into different subsets during tumor development. This transition is influenced by various factors, including signaling molecules released by tumor cells, chemical substances in the TME, and interactions among immune cells.[121] Currently, two main strategies have been adopted in terms of the therapeutic use of neutrophils. First, neutrophils are used as drug delivery carriers. A particularly appealing treatment approach involves using NPs loaded with antineoplastic drugs to target solid tumors. However, most of the drugs applied for this purpose cannot be effectively delivered to solid tumors. Few delivery strategies based on NPs have been successful in clinical practice. Solving the problem of NP delivery will accelerate the clinical applications of nanomedicine. Neutrophils possess remarkable migratory capabilities, allowing them to travel from the bloodstream to different tissues efficiently. This exceptional attribute makes them highly attractive as potential drug carriers, as their ability to target specific tissues can enhance the therapeutic efficacy of treatments.[122,123] In two studies,[124,125] after inducing inflammation, neutrophil-mediated NPs were delivered to the tumor tissue through the vascular barrier, which effectively delivered the therapeutic agents accurately in tumor models. In both studies, neutrophil recruitment required either monoclonal antibodies or photosensitization to stimulate inflammation. Neutrophils could be used to deliver pyropheophorbide NPs or gold nanorods linked to anti-CD11b antibodies to the tumor bed and induce tumor cell death. Neutrophils possess the unique ability to breach the blood−brain barrier and reach inflamed brain tumors, making them advantageous as potential delivery carriers.[126,127] Studies have shown that neutrophils loaded with paclitaxel liposomes can effectively penetrate the brain and inhibit the recurrence of gliomas in surgically resected mice.[128] Pro-inflammatory factors are produced at the resection site, leading to the significant infiltration of neutrophils. Neutrophil-mediated drug delivery effectively prevented recurrence and improved survival rates.

In addition, nanovesicles derived from neutrophil membranes have been developed as drug-delivery tools. Extracellular vesicles are particles defined by lipid bilayers.[129] Researchers have developed a nanoscale neutrophil-simulated drug delivery system comprising neutrophil membrane-coated NPs (NM-NP), which takes advantage of the tumor-homing ability of neutrophils. The NPs are coated with specific ligands or antibodies that recognize receptors or antigens expressed on tumor cells. When injected into the bloodstream, these NM-NPs circulate until they encounter a tumor. Upon reaching the tumor site, the NM-NPs can respond to specific signals in the microenvironment, such as the release of chemotactic factors by the tumor cells. This triggers the NM-NPs to release the encapsulated drugs, enhancing their selective accumulation in the tumor tissue.[130] NM-NPs demonstrated improved cellular interaction under shear flow conditions in laboratory settings compared to uncoated NPs. They also exhibited higher efficiency in capturing circulating tumor cells in live animal models. Through the use of NPs to release chemicals that inhibit immune regulatory cells, such as PD-1, CTLA-4, and other antibodies or RNA interferers, cancer cells can be inhibited to escape immune cell attacks, thus increasing the body's immune response to cancer cells. Nanovaccines prepared using NPs can induce an immune response in cancer cells by showing cancer cell-associated antigens to the immune system. Simultaneously, NPs can also be used as carriers of immune-promoting factors, release various immune-promoting factors, and enhance immune system activity. NPs can target tumor tissue through targeting function, releasing drugs or immune factors that cause immune cells to kill cancer cells, and achieving the targeted killing of cancer cells.

4.3. Regulation of the Interaction between Tumor Cells and the Matrix. Drug delivery systems based on nanomaterials can accurately deliver drugs to tumor cells, reducing damage to the surrounding normal tissues. Surface functionalization of nanomaterials can make them specialized, interact with tumor cells, and achieve directional drug delivery and targeted effects. During the interaction between tumor cells and the matrix, the chemical modification and physical properties of nanomaterials can regulate the microenvironment, including the pH value, redox state, and growth factors. This is achieved through competitive binding and adsorption, which affect the metabolic activity and proliferation of tumor cells and ultimately inhibit tumor growth and metastasis.

5. EFFECT OF NANOTHERAPY ON THE PCa MICROENVIRONMENT

5.1. Effects on the Immune System. Some nanomaterials have been shown to enhance the treatment of PCa by activating the immune system. For example, tumor cells can recognize and ingest some NPs, promoting apoptosis and stimulating the immune system to attack the cancer cells. In addition, some nanomaterials can be designed to inhibit the release of immunosuppressive molecules from tumor cells, thereby increasing the effectiveness of the immune system.

5.2. Effects of Nanotherapy on Tumor Cells. Nanotherapy can have various effects on PCa tumor cells, including directly killing tumor cells, inducing tumor cell apoptosis, and preventing the growth and spread of tumor cells. Some NPs can target specific molecules or surface receptors on cancer cells and enter tumor cells via adsorption, uptake, or infiltration. For example, NPs can release living substances into cancer cells by carrying chemotherapeutic drugs or radioisotopes, resulting in a cytotoxic effect. In addition, some NPs can produce optical, thermal, or mechanical stimulation and can directly kill tumor cells.

5.3. Effects of Nanotherapy on Tumor Vessels. The effect of nanotherapy on tumor vessels in PCa is mainly achieved by changing the TME. Tumors require large amounts of nutrients and oxygen to grow and spread. Therefore, the cells around the tumor guide the peripheral blood vessels to grow and enter the tumor tissue by releasing growth factors and signal molecules, forming abnormal vascular networks, which have the characteristics of irregularity, incompleteness, and abnormal permeability. Consequently, tumor cells can obtain more nutrients and oxygen. NPs can play various roles in tumor blood vessels, resulting in an inhibitory effect on tumor cells. For example, some NPs can change vascular permeability by specifically binding to tumor vascular endothelial cells, thus affecting tumor nutrition supply and oxygen uptake. Additionally, some NPs can be designed to carry tumor cell recognition molecules to target and dissolve tumor blood vessels.

5.4. Effects of Nanotherapy on Tumor Stromal Cells. The PCa matrix mainly includes interactions between the ECM and specific tumor cells. Nanotherapy can affect the

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development of PCa by targeting various components or pathways in the matrix. First, NPs can be designed to be oriented and targeted to certain components of the tumor matrix. For example, some NPs can bind to specific proteins in the tumor matrix, thereby affecting the adhesion and movement of tumor cells. In addition, some NPs can play a therapeutic role by carrying drugs into the tumor matrix. Second, NPs can affect tumor growth and spread by changing the TME. The tumor matrix contains many ECM molecules, which have a strict arrangement and density, and tumor cells rely on these molecules for adhesion, growth, and diffusion.

6. APPLICATION PROSPECT OF NANOTHERAPY IN THE PCa MICROENVIRONMENT

6.1. Preclinical Research. Recently, nanotechnology has become one of the most important research topics in the medical field. As an application in this field, nanotherapy has also received increasing attention. Preclinical studies on nanotherapy targeting the PCa microenvironment have been carried out from various aspects as described below.

6.1.1. NP-Mediated Targeted Delivery of Chemotherapeutic Drugs. Surface modification of nanomaterials allows them to target PCa cells, accurately delivering chemotherapeutic drugs to the lesion site and effectively reduce the toxicity and side effects of drugs in normal tissues. Nanocarriers can be designed using an active-targeting strategy to improve delivery efficiency. This strategy aims to target tumor-specific receptors or ligands that are overexpressed on the tumor or tumor vascular system, thereby enhancing the specificity of drug delivery.[131] For example, a bone marrow-specific transmembrane receptor was designed in which an antibody against CD33 is immuno-coupled with galicamycin to treat acute myeloid leukemia.[132] Other strategies have been reported to enhance targeted drug delivery through endocytosis. These strategies include the use of ligands or antibodies on drug carriers to specifically bind to cell-surface receptors, thereby triggering receptor-mediated endocytosis. Researchers have also delved into the importance of optimizing drug carrier properties such as size, charge, and surface modifications to improve endocytic uptake and intracellular drug release.[133,134] However, tumor cells are likely not able to express specific receptors. Therefore, the overexpression of these receptors indicates tumor-specific characteristics that can be effectively targeted using this approach.[135] Herceptin (trastuzumab) has been successfully used to target the overexpressed HER2 receptors in certain breast cancer subtypes, leading to the development of therapeutic monoclonal antibodies.[136] Moreover, RGD (Arg-Gly-Asp) is a peptide sequence that has high affinity for integrin receptors, which are often overexpressed on the surface of tumor cells and in the tumor neovasculature. When nanocarriers are functionalized with cyclic RGD peptides, they can specifically bind to these integrin receptors. This targeted binding enables the nanocarriers to selectively accumulate in tumor tissues, enhancing drug delivery to the desired site while minimizing off-target effects.[137] Nanocarriers can also be conjugated with cyclic RGD peptides to target new markers in the vascular system, such as α and β integrins or anti-VEGFR.[138,139] Additionally, there are active drug-targeting strategies involving the development of antibodies or ligands that specifically target the prostate-specific membrane antigen (PSMA).[140,141] These strategies have been extensively explored and utilized, with reports of PSMA-labeled liposomes for precise targeting of advanced PCa cells.[142]

6.1.2. Magnetic NP Adjuvant Therapy. Magnetic NP adjuvant therapy uses the unique properties of magnetic NPs, guides and locates them through an external magnetic field, and achieves local treatment of PCa in the microenvironment. Simultaneously, magnetic NPs can be used as imaging probes to help diagnose and locate PCa more accurately.

6.1.3. NPs for PTT. PTT involves wrapping a photosensitive material in NPs to produce a thermal effect by light excitation, thereby achieving local treatment in the PCa microenvironment. In addition, the therapeutic effect can be further improved by osmosis, adsorption, transfer, and removal of NPs.

6.1.4. Nanoenzymology. NPs are also used as enzyme carriers to achieve an accurate enzyme-catalyzed reaction in the PCa microenvironment to achieve the purpose of treatment. Nanoenzymes have good stability, activity, and specificity compared to traditional enzymes.

6.2. Preclinical Experiments Related to Nanotherapy in PCa. An innovative technology exists for the treatment of PCa that utilizes AuNPs and laser-induced thermotherapy to selectively destroy PCa cells in a noninvasive manner. AuNPs are injected into the patient's body and these particles selectively accumulate in the PCa cells. Once the AuNPs are absorbed, the patient's prostate area is exposed to laser light. The AuNPs absorb the laser energy, generating localized heat that destroys the surrounding cancer cells. It is a noninvasive treatment that reduces patient trauma and recovery time compared to traditional surgical removal or radiation therapy. Second, due to the targeted nature of AuNPs, it can selectively destroy PCa cells, minimizing damage to surrounding normal tissues. Although this technology is promising for the treatment of PCa, further studies and clinical evidence are needed to determine its safety and efficacy. Akanda et al. employed a bioconjugation approach to modify solid lipid NPs, enabling them to specifically bind to PCa cells. *In vitro* experiments were used to assess the cellular uptake and toxicity of the NPs, as well as the drug release efficacy. Experiments with a mouse model were further conducted to evaluate the distribution, anticancer activity, and safety of the NPs *in vivo*. The results demonstrated that the bioconjugated solid lipid NPs effectively bound to PCa cells and released the anticancer drugs, achieving targeted therapy. *In vivo* experiments showed that these NPs exhibited good anticancer activity in mice without causing significant toxicity or side effects. These findings thus demonstrated that bioconjugated solid lipid NPs have the potential for the treatment of PCa and provide valuable insights for the further development of targeted nanomedicines for PCa therapy.[143]

Tumor metastasis can occur through both blood and lymph pathways; however, effectively inhibiting blood and bone metastases simultaneously is challenging. In another study, researchers employed ferroptosis nanotherapy to inhibit the metastatic ability of tumor cells. This method involves introducing a special nanomaterial that induces ferroptosis, a distinct form of cell death, to suppress the growth and metastatic potential of cancer cells. This study developed a nanoplatform called DA/RSL3 to facilitate the intracellular codelivery of polyunsaturated arachidonic acid and the GPX4 inhibitor RSL3. This combination induces iron death and reduces resistance to iron death. This form of ferroptosis nanotherapy significantly inhibited the metastatic ability of tumor cells, including hematogenous and lymphatic metastasis.[144]

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6.3. Clinical Application Prospects. Nanotherapy, which utilizes nanomaterials for disease treatment, is an emerging field with promising applications in the clinical management of PCa (Table 2). PSMA has emerged as a particular and sensitive marker for developing targeted nanobased pentachloroanisole delivery systems.[145] Silicon-based NPs can be used as drug delivery carriers for the clinical treatment of PCa owing to their tunable porosity, high surface area, and the ability to load various sizes and chemicals.[146] Selenium NPs exhibit strong antitumor activity. Related studies have shown that activation of miR-155-5p-related pathways inhibits the metastasis of PCa, in which miR-155-5p directly suppresses IOON-B kinase and SMA- and MAM-related protein 2, which play a crucial role in mediating the migration and invasion of nerve cells.[147] Researchers have developed a DNA vector using surface-modified iron-based NPs and utilized this vector containing binuclei to suppress the expression of the oncogene *SLC4A4*, which was selected through screening with bioinformatics methods. Subsequently, they employed the iron-based NPs/plasmid DNA nanocomposite to treat PCa both *in vitro* and *in vivo*. The targeted gene *SLC4A4* exerts a significant impact on PCa cell proliferation. These nanocomposites effectively inhibited the expression of *SLC4A4* and demonstrated potent inhibitory effects on PCa cells *in vivo* and *in vitro*, demonstrating their potential as therapeutic strategies for the treatment of PCa.[148]

Table 2. Potential Applications of Nanotherapy in Prostate Cancer

Nanotherapy	Mode of action	Acting receptors/ targeting genes/ related pathways
Silicon nanoparticles	Drug delivery carrier	Prostate-specific membrane antigen, folic acid receptor, etc.
Selenium nanoparticles	Mediate the migration and invasion of nerve cells	miR-155-5p-related pathway
Iron-based nanoparticles	Inhibition of oncogene expression	Target gene *SLC4A4*
New nanotherapy platforms	Photothermal and photodynamic therapy	Gastrin-releasing peptide receptor

In vivo studies have shown that NPs with good biocompatibility can significantly eradicate prostate tumors. GRPr-mediated photothermal thermodynamics combined with an antiapoptotic mechanism can be used to treat PCa.[149] One of the most important advantages of nanobodies is their temperature, alkali, and acid resistance; therefore, the nanobody method does not require special storage conditions. In addition, the small size of NPs can decrease immunogenicity, improve pharmacokinetics, penetrate tissues more effectively, and improve the targeting energy of hidden epitopes. The similarity between NPs and human antibodies is beneficial for their clinical application in the case of minimal immunogenic reactions. NPs can be used to prepare sensitive biosensors for identifying PCa, immunotoxic drugs, and ADC drugs. The rise in the detection of this cancer type relies on identifying specific antigens such as PSA or PSMA, which are vital markers of PCa. Early detection plays a crucial role in enabling more effective treatment for patients.[150] Jiang et al.[151] combined indocyanine green, with biosafety and diagnostic and therapeutic functions, along with paclitaxel—a highly effective antitumor drug—through weak interaction and ultrasound-assisted synthesis to construct a novel nanodrug without nanocarriers, avoiding the use of methanol and simplifying the NP preparation protocol compared with the solvent evaporation method. Pinhothe et al. reported the treatment of localized prostate cancer using gold nanoparticles combined with laser irradiation. PTT is a minimally invasive and accurate method that has shown promise in treating localized PCA with a favorable safety profile and rapid recovery time. However, the effectiveness of PTT depends on the ability of the light to reach the tumor tissue. AuNPs have proven to be promising PTAs due to their ability to convert energy into heat through their optical characteristics, such as SPR, which occurs in the presence of light at certain wavelengths. Pinhothe et al. synthesized and characterized the AuNPs in terms of size, polydispersity index, zeta potential, morphology, and surface plasmon resonance, as well as AuNP safety and efficacy in PC-3 cells *in vitro*. Incubation of cells with different concentrations of AuNPs significantly reduced cell viability after irradiation compared to nonirradiated samples. Hence, the method was deemed potentially effective for treating PCa.[152]

6.4. Challenges for the Clinical Translation of Nanotherapy. *6.4.1. Controllable and Repeatable Use of Nanotherapy.* There are several challenges to overcome to achieve the widespread clinical application of nanotherapy in cancer treatment. First, the preparation process for NPs is relatively complex and requires precise operations in many steps, such as selecting suitable raw materials, chemical reaction conditions, and surface modification. Small changes in these factors may affect the properties of NPs, thus affecting their therapeutic effects. Therefore, ensuring the repeatability and accuracy of the NP preparation process is critical. Second, the existing characterization technology for NPs cannot fully meet their characterization needs, and there are some defects and limitations in the structure, size, shape, surface properties, and stability of NPs. This may affect the controllability and repeatability of nanotherapy. In addition, the *in vivo* behavior of NPs is a complex issue, as they can be affected by the biological environment, such as the liver, spleen, and lymphatic system. These factors may affect NP drug release behavior and biological distribution, thereby affecting their therapeutic effect. Finally, the safety of nanotherapy is also an issue that needs to be considered. Some nanomaterials may have adverse effects on the human body, such as toxicity and side effects, because NPs have a small size and unique surface properties; therefore, more detailed safety assessments and monitoring are needed in nanotherapy.

6.4.2. Mass Production of Nanotherapy. Current preparation methods for NPs mainly include chemical synthesis, physical methods, and biosynthesis. Chemical synthesis has become a commonly used preparation method because it has the advantages of controllable and large-scale production; however, more research is needed to optimize the reaction conditions and continuous process in the preparation process to improve the preparation speed and reduce the cost. Moreover, the stability of the NPs during preparation, storage, and transmission should also be considered. Owing to the influence of sunlight, moisture, and other factors, NPs may experience problems such as aggregation, decomposition, or crystallization, which may affect their stability and quality. Therefore, in the preparation process, maintaining the stability of the NPs is necessary to ensure that they do not fail during long-term storage and transportation. Finally, the mass

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production of nanotherapy also needs to consider production costs and regulatory requirements. High production costs may limit the scope and scale of mass production, and regulatory requirements need to consider the safety and effectiveness of nanodrugs.

6.4.3. Evaluation and Screening of Nanotherapy. The evaluation and screening of nanotherapy are important to ensure its safety, effectiveness, and clinical application. This process typically includes various steps, as described below.

6.4.3.1. Preparation and Characterization of NPs. The preparation of NPs requires many steps, such as surface modification and size control. Simultaneously, the prepared NPs must be characterized to determine their physical and chemical properties, such as size, shape, surface chemistry, and stability. These factors may affect the biological activity and pharmacodynamics of NPs; hence, they must be characterized and identified in detail. Since NPs can be used as drug carriers to wrap the drug inside and release it at the target site, understanding the drug-release characteristics is critical, including their rate, mechanism, and influencing factors. Simultaneously, needles are required to evaluate the pharmacokinetic characteristics of NPs to determine the metabolism and distribution of drugs in the body.

6.4.3.2. Cytotoxicity and Biocompatibility. The application of NPs must consider their possible toxicity and adverse reactions *in vivo*; therefore, carrying out *in vitro* cell experiments and mouse toxicity tests is necessary to determine the cytotoxicity and biocompatibility of NPs.

6.4.3.3. Drug Efficacy and Clinical Efficacy. NPs are widely used in drug delivery; therefore, evaluating their drug and clinical efficacy is necessary. Animal models and clinical experiments are required to determine NP drug delivery and efficacy *in vivo*.

6.4.3.4. Safety Assessment and Monitoring. NPs have special surface chemical properties and size effects, which may cause toxicity or adverse reactions in the human body; therefore, detailed safety assessments and monitoring are needed. This includes monitoring the biological distribution, toxicity, metabolism, and excretion of NPs in the body to ensure the safety and effectiveness of nanotherapy.

7. CHALLENGES AND PROSPECTS

Reshaping the PCa microenvironment requires NPs to pass through the biofilm and intercellular space to reach the tumor cells. This requires the accurate design and modification of NPs to enhance their targeting and antisolubility. After entering tumor cells, NPs need to overcome various biological obstacles such as low pH, hypoxia, and immune system attacks, which are important challenges. Therefore, changing the physical and chemical properties of NPs to increase their stability and efficacy in tumor cells is necessary. Additionally, the safety of nanotherapy is an important issue in reshaping the PCa microenvironment. Some NPs may exhibit biological toxicity and potential side effects, and rigorous experiments and clinical trials are required to evaluate their safety and effectiveness. Finally, in terms of prospects, nanotherapy is constantly being developed and improved. In the future, intelligent NPs may be developed that can be localized and released in response to specific stimuli such as light, magnets, or sound waves to further improve their targeting and efficacy. These new technologies will, in turn, increase the possibilities of nanotherapy for PCa treatment.

The PCa microenvironment is a complex microenvironment formed by many different types of cells and their interactions. These microenvironments are closely associated with tumor growth, proliferation, and metastasis. New nanotherapy strategies, which are superior to traditional treatments, can improve therapeutic effects and reduce side effects. Treatment of PCa by reshaping the TME has become a research hotspot. Accordingly, we have provided a comprehensive review of the composition and characteristics of the PCa microenvironment and the mechanisms of various nanotherapies. An in-depth understanding of the mechanisms and targets of various types of nanotherapies for the TME will contribute to developing new and effective PCa treatments. New nanomolecules are continuously being developed. Although research progress has been rapid in applying the concept of nanotechnology to the treatment of many types of cancer, only a few preclinical studies based on nanotherapy have focused on prostate tumors to date. PCa has a high incidence in males and a poor prognosis in the event of metastasis. Therefore, studying novel nanotherapy strategies focusing on reshaping the TME of PCa is necessary to improve the treatment, quality of life, and long-term prognosis of patients.

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Notes

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