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Revolutionizing cancer treatment: Nanotherapeutics targeting the tumor micro-environment

Deepak Chandra Joshi [a], Sonima Prasad [b,c,*], Vishal Bhati [d], Pravesh Kumar Sharma [e], Nirmal Joshi [f], Sumit Durgapal [g], Mayuri Bapu Chavan [h], Vishesh Kumar Maurya [i], Vetriselvan Subramaniyan [j], Keshav Raj Paudel [g,k,l,m,**], Madhu Gupta [n,***]

[a] Department of Pharmacy, Faculty of Pharmaceutical Sciences and Nursing, Vivekananda Global University, Jaipur, Rajasthan, India
[b] ICFAI school of Pharmaceutical sciences, ICFAI University Jaipur, Rajasthan, India
[c] Department of Pharmaceutical Sciences, Banasthali Vidyapeeth, Newai, Jaipur, Rajasthan 304022, India
[d] University Institute of Pharma Science and Research, Chandigarh University, Gharuan, Punjab, India
[e] Department of Pharmacy, Faculty of Pharmaceutical Sciences and Nursing, Vivekananda Global University, Jaipur, Rajasthan, India
[f] Faculty of Pharmaceutical Sciences, Amrapali University, Shikha Nagar, Haldwani, Nainital, India
[g] Department of Pharmaceutics, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Premnagar, Dehradun, India
[h] TMV's Lokmanya Tilak Institute of Pharmaceutical Sciences, Pune, Maharashtra, India
[i] Future Institute of Pharmacy, Future University, Bareilly, Uttar Pradesh, India
[j] Division of Pharmacology, Faculty of Medical and Life Sciences, Sunway University, BandarSunway, Selangor Darul Ehsan 47500, Malaysia
[k] Centre for Inflammation, Faculty of Science, School of Life Sciences, Centenary Institute and University of Technology Sydney, Sydney, NSW, Australia
[l] Woolcock Institute of Medical Research, Macquarie University, Sydney, NSW, Australia
[m] NICM Health ResearchInstitute, Western Sydney University, Westmead, NSW 2145, Australia
[n] Department of Pharmaceutics, School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University (DPSRU), New Delhi 110017, India

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ABSTRACT

Precise targeting of the tumor micro-environment (TME) through nanotherapeutic innovations offers a transformative approach to cancer treatment. In order to increase the treatment efficacy, this review delves into the complex tactics for targeting different parts of the TME. Targeting the extracellular matrix, controlling acidosis and hypoxia, and preventing neovascularization by concentrating on pericytes and endothelial cells are important areas covered in this article. Strategies to stimulate anti-tumor immunity, regulate chronic inflammation, and restrict macrophage recruitment emphasize the immune system's participation. We have also highlighted the role of fibroblasts and exosomes linked to the cancer progression. The EPR effect, which is vital for cancer nanotherapeutics to work, and vascular pathophysiology are also included in the review. We examine how changes to the dynamics of pH inside the TME affect by nano-therapeutics. Additionally, the possibility of prodrug therapy within the TME, the use of controlled release mechanisms in nanocarriers to imitate metronomic therapy has been discussed. Lastly, the paper examines nanoparticle preference targeting as a potential strategy to improve treatment specificity and therapeutic efficacy in cancer management.

* Corresponding author at: ICFAI school of Pharmaceutical sciences, ICFAI University Jaipur, Rajasthan, India.
** Corresponding author at: Centre for Inflammation, Faculty of Science, School of Life Sciences, Centenary Instituteand University of Technology Sydney, Sydney, NSW, Australia.
*** Correspondence to: Department of Pharmaceutics, School of Pharmaceutical Sciences, Delhi PharmaceuticalSciences and Research University, Govt. of NCT of Delhi, New Delhi 110017, India.
E-mail addresses: deepakchandra.joshi@vgu.ac.in (D.C. Joshi), sonima.prasad@iujaipur.edu.in (S. Prasad), Vishalbhati429@gmail.com (V. Bhati), pravesh.sharma@vgu.ac.in (P.K. Sharma), nirmal959@amrapali.ac.in (N. Joshi), sumitdurgapal@uumail.in (S. Durgapal), cmayuri7282@gmail.com (M.B. Chavan), Visheshmaurya97@gmail.com (V.K. Maurya), vetris@sunway.edu.my (V. Subramaniyan), keshavraj.paudel@uts.edu.au (K.R. Paudel), madhu@dpsru.edu.in (M. Gupta).

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1. Introduction

Cancer remains a significant and urgent medical challenge worldwide, ranking as the second leading cause of mortality and, in some regions, even surpassing heart disease [1]. Research forecasts that about one-third of the global population will experience cancer at some stage in their lives, highlighting the pervasive influence of this disease [2]. Conventional cancer treatment methods generally encompass multiple modalities, including surgical interventions, chemotherapy drugs, and radiation therapy, or perhaps a mix of these therapies [3]. However, chemotherapy in particular is limited by its lack of selectivity, indiscriminately affecting both malignant and healthy tissues. This non-specific action frequently leads to debilitating side effects and systemic toxicity, ultimately diminishing therapeutic efficacy [4]. Despite the development of diverse therapeutic approaches over the past six decades, survival rates for advanced-stage cancers have shown only modest improvement, reflecting stagnation in progress. This circumstance has highlighted the urgent necessity for the creation of novel anticancer chemotherapeutic drugs, resulting in heightened interest in employing nanotechnology-based delivery systems [5]. Numerous passives, non-active targeted drug delivery systems have received approval to improve the selective efficacy of these medications precisely within malignant tissues. Nanocarrier systems are particularly attractive because they can achieve selective tumor accumulation through both passive and active targeting, thereby enhancing therapeutic efficacy while minimizing systemic toxicity [6]. This process is known as the 'increased permeability and retention' effect, which is a crucial element of tumor therapy regimens. This review aims to synthesize and critically analyze current nanotherapeutic strategies that exploit the enhanced permeability and retention (EPR) effect and active targeting approaches for selective delivery to tumor sites. It will examine different classes of nanocarriers, their physicochemical design parameters, and their application to specific components of the TME, including stromal cells, vasculature, extracellular matrix, hypoxic niches, and immune elements. In addition, preclinical and clinical evidence will be assessed to highlight therapeutic efficacy, translational challenges, and future opportunities for integrating TME-targeted nanotherapies into multimodal cancer treatment regimens. [7]. The main aim of this study is to highlight the benefits, opportunities, and potential of this new generation of agents developed for enhanced cancer diagnosis and treatment [8].

Within this framework, it is crucial to recognize that cancer itself is a highly complex and multifaceted group of diseases, ranking as the second leading cause of mortality worldwide [9]. In recent decades, research and development aimed at identifying effective cancer treatments have made significant advancements, resulting in more successful and less catastrophic outcomes for those diagnosed with this dreadful disease [10]. Currently, cancer treatment may involve several tactics, including hormone medicines that alter endocrine system function or the novel application of genetically modified viruses that specifically target and eliminate cancer cells [11]. Moreover, diverse immunotherapeutic techniques designed to change the body's immune system to enhance its capacity to identify and eliminate cancer cells have demonstrated considerable success in improving patients' quality of life. This accomplishment is seen not only in the enhancement of survival rates but also in the reduction of risks related to recurrences following traditional treatments such as chemotherapy, surgery, and radiation therapy, which are frequently painful [12]. Regardless of whether the therapeutic strategy is explicitly designed to eradicate cancer cells or to modify their surrounding environment, a precisely targeted approach can markedly enhance therapeutic efficacy while concurrently

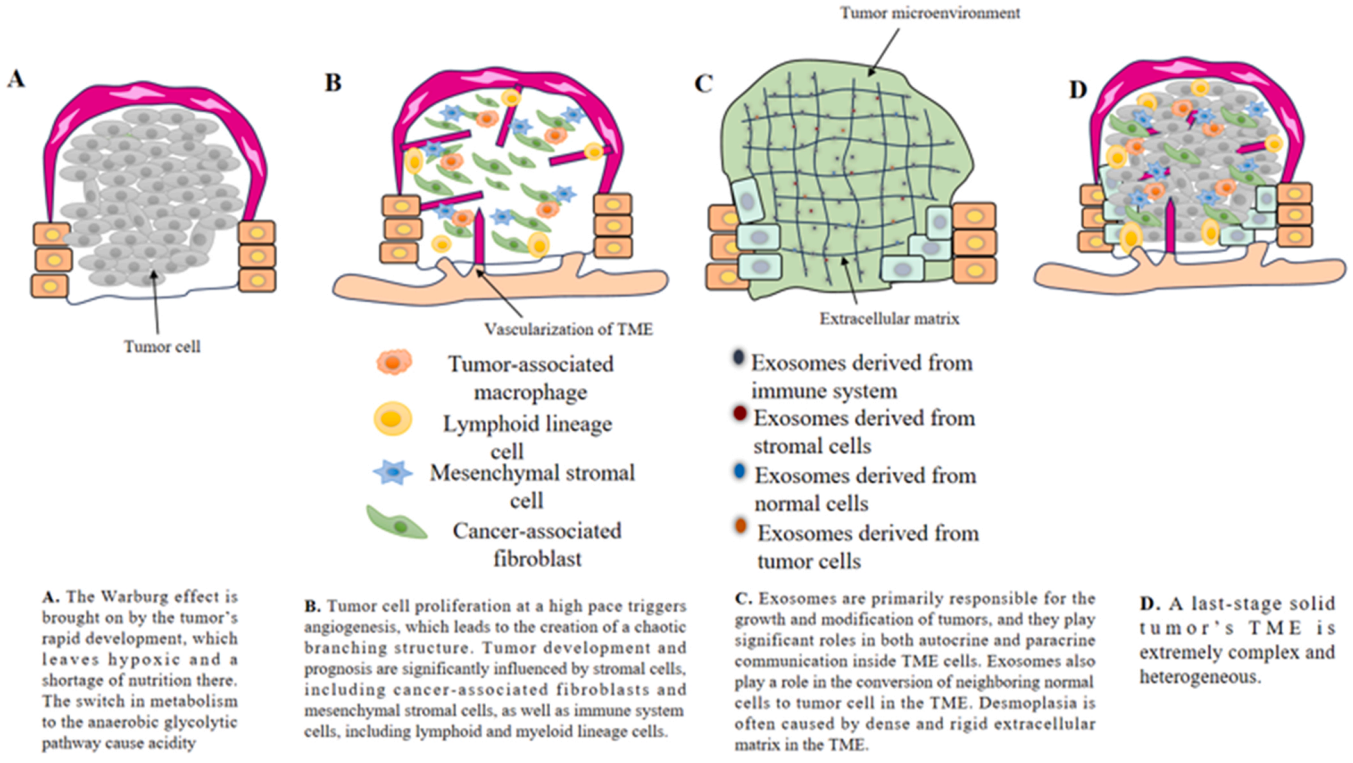


Fig. 1. A. The Warburg effect is induced by the tumor's rapid development, which leaves hypoxic and a shortage of nutrition. The switch in metabolism to the anaerobic glycolytic pathway cause acidity; **B.** Tumor cell proliferation at a high pace triggers angiogenesis, which leads to the creation of a chaotic branching structure. Stromal cells, such as cancer-associated fibroblasts and mesenchymal stromal cells, as well as immune system cells, including lymphoid and myeloid lineage cells, have a substantial impact on tumor development and prognosis; **C.** Exosomes are primarily responsible for the growth and modification of tumors, and they play significant roles in both autocrine and paracrine communication inside TME cells. Exosomes also involved in the conversion of neighboring normal cells to tumor cell present in the TME. Desmoplasia is often caused by dense and rigid extracellular matrix in the tumor site; **D.** In advanced stages, the **microenvironmental milieu** becomes extremely complex and heterogeneous.

minimizing adverse side effects. A recent trend in innovative treatment strategies is nanotherapy, wherein nanodevices are electrostatically linked to therapeutic chemicals and precisely functionalized to recognize and selectively target specific malignant areas [13]. As mentioned below in Fig. 1. This is accomplished by using the unique characteristics of these tissues, like the overexpression of specific receptors, certain pH levels, or the application of physical stresses that are exclusive to analogous locations, hence reducing the likelihood of detection and targeting in healthy tissues [14]. The extensive selection of biocompatible and biodegradable materials for the design of these advanced assemblies is indeed impressive and offers significant prospects. The implementation of multimodal treatment strategies has demonstrated advantageous results in both animal and human models across diverse cancer therapies, including chemotherapy, radiation therapy, phototherapy, immunotherapy, gene therapy, and molecular treatments designed to entirely inhibit the expression of specific proteins in cancer cells [15]. Nanotherapeutics, engineered using direct methodologies to access, infiltrate, and be selectively assimilated by tumor cells, provide the potential to significantly augment the cancer-eradicating efficacy of established therapeutic medicines [16]. The incorporation of previously ineffective medicines into these novel nanotherapeutic designs may signify the next rational and promising advancement in the fight against cancer. Any newly formulated nanotherapeutic must accomplish two critical steps. First, it must attach securely to the biological organism and reach the tumor site reliably. Second, researchers can then properly evaluate its therapeutic benefits in diseased animal models. [17]. Nonetheless, the complexation and intrinsic features of these nanotherapeutics must be meticulously studied and analyzed prior to any shift to in vivo testing. The physicochemical properties of nanotherapeutics fundamentally influence their behavior within the organism, hence defining both their therapeutic efficacy and the potential for harmful effects [18].Despite remarkable progress, nanotherapeutic strategies face critical challenges that continue to hinder their widespread clinical application. The enhanced permeability and retention (EPR) effect, while central to passive targeting, is highly heterogeneous across tumor types and patients, reducing its predictability and reliability. Active targeting approaches also encounter significant obstacles, including immune clearance, limited tumor penetration, and scalability issues in manufacturing. Furthermore, the translation of promising preclinical findings into consistent clinical success remains a major bottleneck, owing to the complexity of the tumor microenvironment (TME), interpatient variability, and incomplete understanding of nanoparticle–host interactions. These gaps bring up the need for continued refinement of nanocarrier design, delivery strategies, and translational studies to fully harness the therapeutic potential of nanomedicine.

This review aims to provide a comprehensive and critical evaluation of nanotherapeutic approaches targeting the tumor necrosis factor (TNF) in cancer. It discusses the TME's components and their role in cancer progression, analyzes nanotherapeutics' principles and advantages, examines various nanocarriers, highlights design considerations for nanoparticles, evaluates delivery strategies, summarizes preclinical and clinical studies, and addresses current challenges and emerging trends in nanomedicine. The review aims to bridge knowledge gaps, identify translation barriers, and highlight opportunities for advancing nanotherapeutics as a next-generation cancer treatment.

1.1. Challenges in traditional cancer treatments

Cancer continues to be a major global health burden, with conventional treatments such as chemotherapy, radiotherapy, and surgery offering only partial solutions due to inherent limitations. Chemotherapy often suffers from poor selectivity and systemic toxicity, as small-molecule drugs are rapidly cleared from the body and indiscriminately affect both healthy and malignant cells [11]. In the case of radiotherapy, significant doses of radiation are often required to accomplish the desired anticancer effects, but this process might mistakenly damage the surrounding normal tissues, producing extra difficulties [19], especially when tumors are located near vital or sensitive organs [20]. Surgical resection, although potentially curative in localized cancers, is restricted to early-stage or easily accessible tumors [21]. In advanced stages or when tumors are located in anatomically complex regions, surgery becomes less effective and carries a higher risk of complications [22].

These limitations collectively underscore the need for alternative approaches that can enhance treatment precision, reduce toxicity, and overcome the shortcomings of conventional strategies.Over the past decade, research on nanotherapeutics has grown substantially, reflecting their transformative potential in cancer treatment. The accumulation effect in nanodrug delivery systems has led to significant enhancements in therapeutic efficacy through thermally enhanced targeting of therapeutic nanoparticles and polymeric particles [23]. For instance, nanoparticles can be engineered to respond to external or internal triggers, such as magnetic fields, to achieve localized targeting. Parameters including particle size, aspect ratio, dose, and exposure time, strongly influence their targeting efficiency [24]. In addition, iron oxide nanoparticles under an alternating magnetic field can induce localized hyperthermia, improve tumor vascular permeability, and facilitate deeper drug penetration. This integrative approach not only enhances therapeutic efficacy but also represents a clear advancement over the systemic and non-specific nature of traditional treatments, thus creating a more logical bridge between conventional oncology and nanomedicine. [25].

2. Understanding the TME

The micro-environment of solid tumors differs from healthy tissues and directly and indirectly influences tumor growth, angiogenesis, invasion, and metastasis. The tumor microenvironment (TME) is composed of a heterogeneous mixture of cell types such as cancer-associated fibroblasts, endothelial cells, pericytes, and infiltrating immune cells (e.g., macrophages, T cells, and dendritic cells), along with the extracellular matrix (ECM) and soluble signaling factors like cytokines, chemokines, and growth factors, which together regulate tumor progression. The diverse cellular population within the TME presents numerous potential targets for drug delivery [26]. Nanoparticles optimized for substantial accumulation at tumor sites, surface modifications for cellular targeting, controlled drug release, and high loading capacity for the simultaneous engagement of multiple biological components such as tumor cells, stromal cells, and immune cells within the TME to enhance therapeutic efficacy and therapy are nearing clinical application [27]. Several anticancer agents targeting the TME are already in clinical use, for example, Lenvatinib disrupts tumour vasculature by inhibiting VEGFR/FGFR, while immune checkpoint inhibitors such as Avelumab (PD-L1 blocker) and Cemiplimab (PD-1 blocker) restore antitumour immunity within the TME [28].

Multiple studies have demonstrated improved therapeutic efficacy by integrating chemotherapeutic agents with nanoparticles that simultaneously target two or more cell types within the heterogeneous tumor ecosystem, surpassing the effectiveness of single-target strategies [29]. Besides direct therapeutic interventions, nanoparticles may elicit innate and adaptive immune responses, potentially augmenting therapeutic efficacy [30]. Although numerous therapeutic strategies aimed at the TME are presently undergoing rigorous development and evaluation, a deeper understanding of the cellular and molecular mechanisms within the TME is critical. Such knowledge is indispensable for the rational design of combined therapeutic strategies capable of overcoming tumor resistance, thereby reinforcing the central importance of studying the TME in advancing next-generation cancer therapies [31].

2.1. Components of the tumor micro-environment

The TME is a complex and dynamic system including a wide variety of stromal cells, intricately entrenched within the extracellular matrix

surrounding the tumor [32]. This very complex assembly of stromal cells primarily consists of fibroblasts and endothelial cells, in addition to other immune cells and pericytes that collectively perform essential supportive functions in tumor growth. The principal variables contributing to the unfavorable prognoses associated with pancreatic ductal adenocarcinoma (PDAC) are the exceptionally elevated levels of desmoplasia (a fibrotic reaction characterized by excessive ECM deposition and fibroblast activation) that define the stroma surrounding the tumor [33]. This dense stromal response not only acts as a physical barrier that limits drug penetration but also contributes to local immunosuppression by restricting immune cell infiltration. This milieu functions as a significant physical barrier and a complex biochemical niche, including diverse signaling molecules and actively secreting chemokines [34]. These chemokines are essential for recruiting T-regulatory cells and myeloid-derived tumor-associated macrophages (TAMs, a specialized subset of macrophages that adopt a tumor-supportive M2-like phenotype) [C16]. These TAMs further secrete factors that suppress anti-tumor immune responses and promote tumor proliferation. The recruitment of myeloid cells markedly amplifies the tumor's invasive properties, hence complicating the therapy landscape [35].

To provide a clearer and more cohesive understanding of the immunosuppressive mechanisms within the TME, it is important to consider how stromal cells, macrophages, and reactive oxygen species (ROS) function in a coordinated manner [36]. Activated stromal fibroblasts, along with the ECM they produce, create a dense structural and biochemical barrier that not only obstructs the physical infiltration of immune cells but also secretes ligands and enzymes that polarize macrophages toward an immunosuppressive M2 phenotype. These macrophages, along with other myeloid-derived suppressor cells, secrete anti-inflammatory cytokines and additional factors that dampen cytotoxic immune activity. [37]. Concurrently, elevated levels of ROS released by myeloid suppressor cells induce apoptosis in effector T lymphocytes, further preventing the host immune system from effectively targeting the tumor [38]. Together, these interconnected processes establish a highly immunosuppressive microenvironment that enables tumor cells to evade immune surveillance and promotes disease progression [39].

The multifaceted nature of the TME has direct implications for clinical practice. Its dense stroma, immunosuppressive cell populations, and abnormal vasculature collectively contribute to resistance against standard chemotherapies and immunotherapies, posing significant therapeutic challenges. Consequently, a deeper understanding of these mechanisms is critical for developing strategies that can remodel the TME and enhance treatment efficacy.

2.2. Role of TME in cancer progression

The TME is a complex ecology that significantly influences cancer growth. The complex interplay and dynamic relationship between the intrinsic cellular components of cancer cells and the extrinsic stromal cells substantially influence the development of a conducive TME [40]. The environment is influenced by various secreted soluble factors and the extracellular matrix (ECM), which together foster conditions that promote tumor growth, enhance aggressiveness, increase invasive potential, facilitate immune evasion, and ultimately contribute to therapeutic resistance in cancer treatments [41]. A major contributor to this resistance is the abnormal biophysical state of tumors. Inadequate vascularization, elevated interstitial stress, and increased intratumoral fluid pressure all interfere with efficient drug distribution [42]. Such conditions reduce perfusion and limit the delivery of chemotherapeutic agents to deep tumor regions. They also compromise radiotherapy and immunotherapy efficacy by restricting oxygen and nutrient flow, both of which are critical for these treatments to function optimally. Thus, the physical and biochemical characteristics of the TME form a combined barrier that conventional therapeutic approaches must overcome. Within this specialized milieu, perivascular niches host bone marrow–derived cells and other supportive stromal elements that further sustain tumor growth [43].

Macrophages, an immunological component that plays an important role in TME dynamics, are produced from monocytes in the bone marrow and stand out among these populations [44]. Mesenchymal stromal cells, cancer stem cells, tumor-associated macrophages, neutrophils, mast cells, T regulatory cells, effector T cells, and myeloid-derived suppressor cells are only a few of the immune cell types found and active in this milieu [45]. Each of these populations contributes distinct signals and functions that together establish an immunosuppressive and tumor-supportive niche, compounding the challenges of effective treatment delivery [46].

In conclusion, fluid accumulation in malignant tumors results in elevated interstitial fluid pressure. This increased pressure constricts the existing blood arteries, obstructs the removal of waste products in the microenvironmental niche, and impedes the administration of therapeutic medications [47]. Moreover, elevated interstitial fluid pressure impacts the endothelial cell barrier and undermines the establishment of tight connections among these cells. Consequently, even potent systemic therapies often fail to reach their intended intratumoral targets, which explains why tumors with elevated interstitial pressure are notoriously treatment-resistant [47]. The fluctuation in interstitial fluid pressure is a mechanism contributing to vascular normalization and intratumoral hypoxia, resulting in an environment that is less responsive to radiation and chemotherapy [48]. Typically, in the early phases of carcinogenesis, the tumor experiences hypoxia, accompanied by an increase in neovascular formation inside the perivascular niche. This neovasculature originates from adjacent pre-existing vessels and does not augment the blood supply to the tumor tissue. Proliferating cells undergo fast division, and when the tumor exceeds 1–2 mm in diameter, inadequate oxygenation to the center hypoxic area results in central necrosis [49]. These hypoxic and necrotic changes are not only hallmarks of tumor aggressiveness but also underscore the therapeutic importance of the TME. Understanding and targeting these features of abnormal vasculature, oxygenation deficits, and pressure gradients is essential for designing novel treatment strategies, thereby providing a rationale for the TME-targeted therapeutic approaches.

3. Nanotherapeutics in cancer treatment

Cancer nanomedicine has shown significant progress in recent decades. Comprehensive investigations and research initiatives focused on the nanodelivery of chemotherapeutics have revealed considerable potential efficacy for cancer treatment by markedly improving pharmacokinetics, biodistribution, and tumor accumulation of diverse payloads [50]. This enhancement results in greater therapy efficacy while reducing off-target and systemic side effects typically linked to conventional medications. The recent swift advancement of our understanding of the TME has led to notable progress in the creation of novel nanocarriers specifically engineered for the delivery of diverse therapeutic agents targeting cancer treatment [51].

Researchers can now intelligently create enhanced nanocarriers customized to specific compositions and unique physicochemical features, thanks to a more profound understanding of the evolutionary and dynamic processes that define the Tumor ecosystem [52]. These meticulously designed nanocarriers can adeptly traverse numerous biological barriers, enabling them to efficiently isolate and transport several therapeutic drugs directly into the TME, thus promoting enhanced treatment outcomes [53]. The swift advancement of nanoparticle-based drug delivery technologies in recent decades has considerably expanded the array of treatment methods for addressing cancer. The majority of research in this nascent sector has concentrated on the creation of specific nanocarriers infused with chemotherapeutics or biologics [54]. These advances seek to augment medication accumulation precisely within tumors by fully leveraging the established improved permeability and retention impact. Formulations such as

liposomes (e.g., Doxil and Onivyde) are nanoscale vesicles composed of phospholipid bilayers that encapsulate chemotherapeutics, allowing for prolonged circulation time and reduced toxicity. Similarly, albumin-bound nanoparticles like Abraxane utilize endogenous albumin to improve solubility and tumor uptake of drugs such as paclitaxel. These platforms have demonstrated enhanced tumor targeting and clinical benefit compared to conventional formulations, underscoring the translational impact of nanocarrier technology. The efficacy of targeted drug delivery systems is exemplified by the clinical success and progress observed with liposomal formulations of established medications like Doxil, Onivyde, and Abraxane [55]. Notwithstanding these achievements, it is crucial to acknowledge that nanocarrier delivery systems have historically encountered obstacles, including variable clinical efficacy when compared to free drug formulations, limited tumor penetration due to heterogeneous vascularization, manufacturing and scalability challenges, and potential immunogenic or hypersensitivity reactions induced by the carrier materials. Current research is actively addressing these issues through strategies such as surface modification (e.g., PEGylation) to evade immune clearance, ligand-mediated active targeting to improve tumor specificity, and the development of stimuli-responsive carriers that release drugs selectively within the tumor microenvironment. These innovations aim to overcome past limitations and improve therapeutic consistency and patient outcomes. [56]. Recent advancements in tumor development, as well as insights into the cellular and acellular components of the TME, alongside significant breakthroughs in nanomaterial engineering, have created new opportunities for utilizing nanocarrier-based delivery systems to target specific anti-tumor mechanisms in cancer treatment [57]. The various cancer therapy approaches that focus on the tumor micro-environment as mentioned in Figure. 2 below.

3.1. Introduction to nanotherapeutics

The rapid progress in nanotherapeutics for cancer therapy is evident from the surge of publications and reviews, underscoring their significant impact on cancer research. [58]. It has been widely acknowledged that nanocarrier-based drugs have the potential to improve drug stability, optimize pharmacokinetic profiles, and minimize adverse effects. The advancement of clinical development and initial achievements in the treatment of solid tumors have significantly stimulated industry interest in the development of nanodrugs [59]. There are several limitations associated with cancer cell-based drugs, endothelial-targeted angiogenic blocking agents, and T-cell-based immunotherapy drugs. Conversely, the early approval of passive targeting liposomes and imaging nanoparticles has contributed to demonstrating the safety of certain nanocarriers utilized in human applications [60]. This proposal outlines the use of nanotherapy to transform TME, enhancing the direct interaction between drugs and cancer cells to meet somatic needs better. There has been a shift in focus from the development of the nanocarrier, the EPR effect, and the attributes of pharmaceutical nanoformulations to the impact of the nano-induced MVD-lowered TME within a complex, multifaceted, and interactive biological system. This will be the central theme of future research in cancer nano-therapy [61].

3.2. Advantages of nanotherapeutics in cancer treatment

In recent decades, cancer has been projected to become the predominant cause of mortality in both industrialized and developing nations. At now, surgery, chemotherapy, and radiotherapy constitute the conventional therapeutic modalities employed to pursue cancer remission [62]. Nonetheless, these methodologies include limits and often result in toxicity and significant adverse effects. Recent advances highlight nanotherapeutics as a transformative strategy that enhances therapeutic precision and outcomes across diverse cancer types. These approaches are applied both independently and synergistically with conventional treatments, offering greater selectivity and reduced systemic toxicity [63]. We delineate nanotherapeutic approaches for several cancer types inside the TME, focusing on targeted techniques, drug delivery, and therapeutic combination therapies [64].

Cancer is a degenerative disease that is proliferating in prevalence, attributed to aging and environmental factors [65]. Most current cancer therapies, including chemotherapy, radiation, and surgical resection, primarily target the eradication of cancer cells; however, they do not address the complete TME, which is crucial for tumor sustenance and progression [66]. Consequently, therapies may result in significant side effects due to the detrimental impact of antineoplastic drugs on essential organs, cells, and tissues. In recent years, numerous nanoscale delivery strategies have been proposed to facilitate the efficient transport of antineoplastic medicines [67]. Through active targeting and the heightened permeability and retention effects characteristic of the TME,

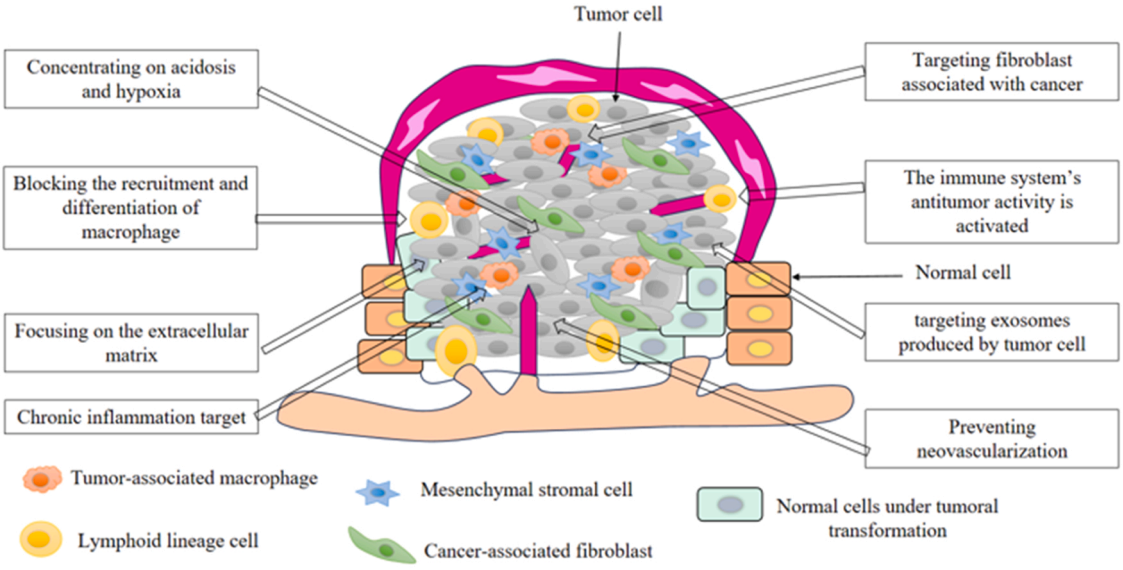


Fig. 2. Cancer therapy approaches that focus on the tumor micro-environment.

nanotherapeutics can selectively accumulate at tumor locations to augment therapeutic efficacy. Furthermore, the amalgamation of therapeutic drugs and nanocarriers to create nanotherapeutics possesses the additional benefit of effectively remodeling the tumor niche while concurrently delivering potent antitumor effects. Strategic integration of chemotherapy, radiotherapy, gene therapy, and immunotherapy with nanocarrier platforms enables a coordinated multi-target attack on tumors. Such combinations improve drug penetration and retention within the TME, boost immune activation, and overcome therapeutic resistance, collectively leading to superior clinical outcomes [68].

4. Types of nanocarriers used in cancer treatment

Nanocarriers transport anti-tumor substances such as chemodrugs, genes, photosensitizers, and proteins in nanoscale approaches to cancer treatment, which are also known as nanotherapeutics or nanomedicines [69]. These have emerged in the last 20 years. Nanoparticles have shown great promise in both preclinical and clinical trials because of their capacity to gather at tumor sites, penetrate cancer cells, and then release their cargo in response to signals from the TME [47]. The effectiveness of nanotherapeutics in preventing or killing cancer cells has been extensively studied thus far. Unfortunately, there has been little discussion of nanoparticles' ability to alter TME in a way that enhances therapeutic efficacy for tumors that are resistant to drugs [47]. Our goal here is to highlight how nanocarriers can regulate the TME. This includes lowering drug efflux in cancer cells, changing the components of the extracellular matrix, and dealing with the immunosuppressive TME [70]. By improving blood supply, we can alleviate hypoxia and treat metastasis. This could lead to the total inhibition of primary and secondary tumor growth, which would open the door to other cancer treatment strategies [71].

Selective and specific binding to cancer cells or certain types of cancer cells, as well as delivery of the active moieties to the cancer cells, are preferred qualities of nanoscale cancer therapeutic agents [72]. Micelles, polymeric nanoparticles, inorganic nanoparticles, protein-based nanoparticles, and liposomes are some of the nanocarriers that have been produced for the treatment of cancer. These nanocarriers are engineered to exhibit either extended circulation, passive targeting, active targeting, or a mix of these and other characteristics [73]. The most effective nanocarriers available for cancer treatment at the moment are micelles, polymeric nanoparticles, and liposomes. These nanocarriers have been successful in translation, but they still face a number of obstacles, such as immune detection, low drug loading, and premature drug release [23]. Immune detection often results in rapid clearance of nanoparticles by the mononuclear phagocyte system, which reduces their circulation time and therapeutic benefit. Low drug loading limits the amount of active drug that can be delivered per carrier, necessitating higher doses and potentially increasing systemic toxicity. Premature drug release can occur due to instability of the carrier in the bloodstream, leading to off-target effects before the nanocarrier reaches the tumor site. Addressing these issues and further increasing the therapeutic efficacy of nanoparticle-based cancer treatment requires new types of formulations and new properties of nanocarriers [74].

4.1. Liposomes

Liposomes are incredibly flexible systems that may encase hydrophilic and hydrophobic substances. They are made up of one or more lipid bilayers. Lipidic bilayers can entrap hydrophilic chemicals in their watery compartments or even contain hydrophobic substances themselves [75]. In theory, liposomes could dissolve hydrophobic drugs, store them for later release, shield them from degradation or alteration, limit their nonspecific interactions with other tissues, enhance their accumulation within tumor tissues through passive or active targeting, or speed up their release at the target site [76]. They can be imbued with compounds that enable them to target tumor cells, activate molecules within the tumor environment, regulate drug delivery, or be imaged at their precise location. To control how the tumor's blood vessels react to radiation, liposomes can transport medications to the endothelium [77]. One can adjust their dimensions, bilayer makeup, bilayer length, and bilayer quantity to target specific cell types, such as cancer cells, tumor cells, stem cells, or the microenvironment surrounding tumors. Many of these promising nanomedicines are now available to patients, and even more are shown encouraging results in clinical trials. Importantly, beyond preclinical promise, several liposomal formulations have already reached clinical practice, reinforcing their translational significance. Commonly available liposomal drugs include Doxil®/Caelyx® (PEGylated stealth liposomal doxorubicin for ovarian cancer, multiple myeloma, and Kaposi's sarcoma), DaunoXome® (liposomal daunorubicin for AIDS-related Kaposi's sarcoma), DepoCyt® (pH-sensitive liposomal cytarabine for lymphomatous meningitis), Marqibo® (liposomal vincristine), Onivyde® (liposomal irinotecan), and Vyxeos® (dual liposomal formulation of daunorubicin and cytarabine) [78].

4.2. Polymeric nanoparticles

A diverse array of polymeric nanoparticles has been created and utilized in cancer research. They are capable of transporting anticancer pharmaceuticals, imaging agents, gene therapy agents, or biomolecules [79]. The polymers extensively researched for the synthesis of polymer nanoparticles include poly (D, L-lactic-co-glycolic acid), polyethylene glycol, poly (N-isopropylacrylamide)-b-poly(L-glutamic acid), block copolymers of poly(ethylene glycol)-poly(aspartic acid), and cationic chitosan [80]. The introduction of polymer–metal hybrid nanoparticles in cancer research has garnered significant attention for its efficacy as multimodal imaging agents [81]. To reinforce clinical relevance, several polymer-based nanomedicines have advanced into clinical trials or obtained approval. For instance, Genexol®PM, Paclical®, Nanoxel®M have reached the market. Among them, Genexol®PM represents the first paclitaxel-loaded polymeric micelle formulated with mPEG–poly(D, L-lactide) (PDLLA), and it has received approval for the treatment of breast and lung cancers [82].

Numerous therapeutically utilized and nanoscale pharmaceuticals have been produced, significantly enhancing the quality of life for thousands of cancer patients since the early 21 st century [83]. They can be classified as small molecular drugs, liposome-based pharmaceuticals, polymer nanoparticle-bound drugs, and drug-protein complexes. They have mostly enhanced the administration, water solubility, drug bioavailability, pharmacokinetic characteristics, and toxicological adverse effects of pharmaceuticals [84]. Recent review papers exist; nevertheless, their practical applicability in tumor-affected animals or human patients have not been adequately delineated at a single cellular resolution. Reviews from over twenty years ago suggest that 21st-century articles mostly concentrated on surface modification and cross-linking techniques to enhance the drug delivery efficacy of polymeric nanoparticles [85].

4.3. Metallic nanoparticles

Nanotherapeutics exhibit versatility in cancer treatment owing to their distinctive capacity to traverse several biological barriers, including blood vessels, capillary interstices, and inter-endothelial cell junctions, facilitated by the improved permeability and retention effect [86]. Diverse metallic nanoparticles have been developed for oncological imaging and therapy. Gold-based nanoparticles exhibit significant light absorption capabilities, resulting in elevated localized temperatures suitable for photothermal therapy, and possess substantial X-ray attenuation properties for imaging purposes [87]. Moreover, when integrated with various imaging modalities, a unified platform can provide image-guided therapy for precise localization and real-time assessment of therapeutic responses [88].

In contrast to drug-loaded nanoparticles, radiotherapeutic agents,

notably gold nanoparticles, demonstrate significant radiosensitization properties that enhance the efficacy of tumor radiation treatments, including X-ray, gamma rays, and high-energy electrons [89]. Metal nanostructures, including gold, silver, and iron nanoparticles, exhibiting strong surface plasmon resonance have been engineered for photothermal therapy. Their high light-to-heat conversion efficiencies can facilitate intratumoral temperature increases within therapeutic ranges of 40–44 °C, enabling cancer treatment through minimally invasive techniques [90]. Magnetite iron oxide nanoparticles serve as alternative hyperthermia agents owing to their superparamagnetic properties, enabling temperature modulation via an alternating magnetic field [91].

However, despite their therapeutic promise, the toxicity and biocompatibility of metallic nanoparticles remain critical considerations. Issues such as oxidative stress induction, mitochondrial dysfunction, genotoxicity, and pro-inflammatory responses have been reported, particularly with silver and iron oxide nanoparticles at higher concentrations [91]. Surface charge, size, and aggregation tendency can significantly influence biodistribution and clearance, with small nanoparticles (<10 nm) often undergoing rapid renal excretion, while larger ones accumulate in the liver and spleen. To mitigate these challenges, surface modifications (e.g., PEGylation, biomolecule conjugation, or coating with biocompatible polymers) are employed to improve circulation time, reduce nonspecific interactions, and enhance tumor selectivity. Rigorous preclinical evaluations and long-term toxicity studies are therefore essential to ensure that metallic nanoparticles achieve a balance between therapeutic efficacy and biosafety.

4.4. Exosome-based nanocarriers

Exosomes secreted by tumor cells serve as a critical interface between the tumor and surrounding cells, drawing significant attention for their role in facilitating tumor growth [92]. Exosomes have been engineered to function as efficient proteolipid drug carriers that target recognition molecules on recipient cells. Exosome-based nanocarriers utilize the inherent targeting capability of exosomes to deliver drugs efficiently and specifically to recipient cells, thereby enhancing the internalization of their drug payloads [93]. The integration of advanced biological techniques and exosome engineering, such as protein superlattices and chip technologies, has facilitated the customization of exosomes into high-yield nanosized synthetic variants with desirable biological properties and biocompatibility, utilizing suitable cell sources [94].

Exosomes, as bio-signaling carriers derived from parent cells with a natural biophysiological lipid bilayer, enhance the loading efficiency of drugs compared to unencapsulated formulations [95]. They also mitigate issues related to nonspecific distribution, exosomal entrapment, rapid blood clearance, and off-target drug delivery. Functionalized exosomes enhance drug precision, resulting in a diminished adverse effect profile and reduced drug toxicity compared to non-exosomal alternatives [96]. To replicate the structure and function of bio-derived exosomes, bio-inspired formulations including liposomes, polymersomes, and protein superlattices have been created. Exosomes have been classified and studied for their roles and effects related to epithelial-mesenchymal transition (EMT), metastasis, cancer immunity, therapeutic resistance, and redox homeostasis [97]. Conversely, these studies establish a significant basis for the proteomic classification of diverse exosome types derived from various donor cells [98].

In terms of clinical translation, exosome research remains in the early stages. Most trials are still observational, focusing on exosomal biomarkers for diagnosis and treatment monitoring in colorectal (NCT04394572), gastric (NCT05334849), lung (NCT03830619), and breast cancers (NCT05955521). A smaller number of interventional trials are exploring therapeutic applications, such as plant-derived exosomal curcumin delivery for colon cancer (NCT01294072), MSC-Exos loaded with KrasG12D siRNA in metastatic pancreatic cancer (NCT03608631, Phase I), and dendritic cell-derived exosomes for advanced non-small cell lung cancer (NCT01159288, Phase II).(ClinicalTrials.gov)

5. Design and development of nanotherapeutics

The design and development of precisely targeted therapeutic drugs are essential for effective cancer imaging and treatment [99]. The intricacy of the TME indicates that monotherapy aimed at a singular cellular or molecular target may prove ineffective in the treatment of specific cancer forms [100]. Conversely, contemporary cancer treatments exhibit considerable adverse consequences. This difficulty has stimulated the creation of sophisticated multifunctional nanotherapeutics aimed at a comprehensive treatment strategy [101].

The design and development of therapeutics aimed at the TME encompass several elements, including a comprehensive understanding of optimal in vivo properties, interactions between therapeutic agents and subjects, key pathological features present in the TME, characteristics of therapeutic agents that facilitate interaction with the target TME, classifications of therapeutic agents, and potential combinations of therapeutic agents for multimodal treatment approaches [102]. Various technologies and procedures have been developed to design and prepare carriers for the transport of drug molecules, gene molecules, or photosensitizers to the TME for chemotherapy, gene therapy, or photodynamic therapy [103]. Their composition encompasses liposomes, micelles, polymeric conjugates, dendrimers, inorganic nanoparticles, and biological drug carriers, including viruses and cell-based delivery systems. These carriers have enhanced the efficacy of the delivered therapeutic agents compared to conventional small-molecule drugs typically utilized in treatment [104]. Nonetheless, obstacles persist in the development of delivery systems that are entirely tuned at the molecular and cellular levels while concurrently addressing the in vivo characteristics required for achieving optimal therapeutic efficacy [105].

6. Types of nanoparticles used in nanotherapeutics

Nanoparticle-based drug delivery systems have distinctive characteristics, including a high surface area to volume ratio, chemical tunability, improved bioavailability, minimal cytotoxicity, and the capacity to encapsulate and safeguard medicines against immune destruction during in vivo administration [106]. All these enhance the effective treatment of diseases and the precise targeting of medications to specific locations. A variety of nanoparticles have been engineered for the treatment of several diseases, including cancer and inflammatory conditions, such as liposomes, polymers, micelles, lipoplexes, and gold and silica nanoparticles [107]. Liposomes, which are either single or multilamellar lipid vesicles, are synthetic lipid nanoparticles made from phospholipids or cholesterol, exhibiting significant versatility in drug delivery applications [108]. Polymers with hydrophobic and hydrophilic segments generate hydrogel structures utilized in nanoscale drug delivery systems, either as amphiphilic blocks or in Dalby matrix configurations. Micelles are diminutive nanoparticles of between 10 and 100 nm in diameter, characterized by a distinctive hydrophilic outside and a hydrophobic interior [109]. Lipoplex systems consist of densely packed nanoparticles associated with a lipid core, enhancing the durability and biological efficacy of the nanoparticles while minimizing cytotoxicity for effective therapeutic delivery. Gold and silica-based nanoparticles are presently being extensively investigated for cancer diagnosis and treatment [110]. Gold nanoparticles can be engineered or synthesized to selectively adhere to cancer cells or target particular areas. High-energy photons can stimulate luminous gold nanoparticles to augment X-ray therapy for cancer. Silica nanoparticles can selectively target, detect, and treat cancer using diagnostic and therapeutic methods [111].

A table delineates the many forms of nanoparticle-based therapies and imaging employed in nanomedicine [17]. Nanoparticle components

can be classified into several primary groups, including proteins, antibodies, small molecular medicines, nucleic acids, endogenous peptides, and drug-sensitive polymers, which facilitate nanoparticle accumulation in the TME [112]. The TME is defined by permeable blood vessels, elevated negative interstitial pressure relative to other organs, and a dysfunctional lymphatic system, which collectively facilitate increased nanoparticle accumulation [113]. Several nanotherapeutics are presently undergoing approval or clinical trial phases for cancer treatment, including Ambirix, Doxil, Camptosar, Abraxane, and Marqibo. These nanotherapeutics presently function as a clinical standard for cancer treatment and imaging [114]. An Overview of Nano-Therapeutic Agents in Cancer Treatment for Targeted Cancer Types is mentioned below in Table 1.

6.1. Functionalization of nanoparticles for targeting TME

A key strategy in nanomedicine involves the functionalization of nanoparticles to overcome the complex barriers presented by the tumor microenvironment (TME). Functionalization enhances nanoparticle stability, prolongs circulation time, improves penetration across dense extracellular matrices, and enables active targeting of tumor-associated components such as hypoxia, stromal cells, and angiogenic vasculature. By tailoring nanoparticles with ligands, peptides, enzymes, or stimuli-responsive features, researchers can significantly improve specificity and therapeutic efficacy while minimizing off-target effects. Thus, functionalization represents a crucial step in translating nanocarriers into clinically viable solutions for cancer treatment. Various targeting moieties can be identified for the TME, including ligands for lymphatic vessels, ECM, stromal cells, and tumor cells with high expression levels of these molecules [115]. When taking the EPR effect into account, it is important to keep in mind that molecules should not be larger than 60 kDa, or 5 nm, in order to accumulate efficiently in tumor tissue [116]. Hypoxia, a common symptom of cancer, is linked to a more aggressive growth potential and reduced sensitivity to radiation and chemotherapy. There has been extensive research on hypoxia-specific drug delivery for many years [117]. The hypoxic environment can be used to one's advantage by creating poisonous organisms, which in turn release the drug at hypoxic locations. Researchers have shown that in a hypoxic environment, PEGylated liposome-encapsulated doxorubicin demonstrates a structural alteration of nitro groups [118].

Systems that are redox-sensitive and have a high intracellular concentration of glutathione have been created with hypoxia targeting. Compared to normal cells, tumor cells have a GSH content that is one hundred times higher [119]. At the tumor site, doxorubicin liposomes self-quench, and then, when the concentration of glutathione (GSH) in the targeted tumor cells is high, they release their contents gradually [120]. Thiol-functionalized poly(lactic-co-glycolic acid) nanoparticles have shown promise as an in vivo breast cancer xenograft agent. We developed a pair of peptides that specifically target angiogenic plasma in the TME of tumor cells and vascular endothelial cells [121]. The amphiphilic conjugates were created using the angiogenic receptor recognition sequences and mesenchymal stem cell nests found on tumor tissues. When mixed with water, they can assemble to produce nanoparticles. Although it failed to interact with HUVEC cells that were not exposed to either peptide, the combination showed a strong affinity for HUVEC cells that had both peptides [122]. In addition, the mixture showed targeted fluorescence imaging at a specific dosage, which suggests a strong affinity for angiogenic plasma and a powerful anti-tumor effect in an in vivo animal model of breast cancer [123].

Table 1
Comprehensive Comparison of Normal Cells, Cancerous Cells, and Cancer Cell Lines.

S. N.	Normal Cell	Cancerous Cell	Cancer Cell Line	Reference
1	Breast	Breast Glandular	MCF−7	[50]
2	Colorectal	Colon Glandular	HCT116	[51]
3	Renal	Kidney Glomeruli Kidney Tubular	HEK293	[52]
4	Lung	Lung Alveolar	A549	[53]
5	Ovarian	Overy Stromal	OVCAR	[54]
6	Urothelial	Urinary Bladder	T_{24}	[55]
7	Cervical	Cervix Squamous	HeLa	[56]
8	Liver	Liver Hepatocyte	$HepG_2$	[57]
9	Pancreatic	Pancreas Islet	HuP-T_1	[58]
10	Skin	Skin Epidermal	A431	[59]
11	Stomach	Stomach Glandular	HGT−1	[60]
12	Thyroid	Thyroid Glandular	P_2X	[61]

6.1.1. Targeting the extracellular matrix

The extracellular matrix is a crucial element of the TME that significantly influences resistance to cancer therapy, tumor advancement, and unfavorable prognosis [70]. The excessive deposition, atypical composition, heightened stiffness, and disordered architecture of cancer extracellular matrix impede the diffusion and penetration of treatments.

To address this, enzymatic and physical functionalization strategies have been developed. Collagenase degrades fibrillar collagen, reducing matrix stiffness and improving drug penetration, while hyaluronidase breaks down hyaluronic acid, lowering interstitial fluid pressure and facilitating deeper diffusion of nanocarriers. In contrast, photoactivatable agents rely on external light to generate localized heat, ultrasound-induced cavitation, or reactive oxygen species (ROS), which cause matrix degradation and transiently open diffusion pathways. Collectively, these mechanisms weaken the ECM barrier and enhance intratumoral accumulation of therapeutics. Modified nanoparticles, macromolecules, and biological cells that produce collagenase and hyaluronidase to dissolve the extracellular matrix have been found and shown to enhance the distribution of therapeutic drugs to tumors and improve tumor therapy [124]. Alternatively, photoactivatable agents can utilize light to induce heat, sonolysis, or generate reactive oxygen species to degrade the extracellular matrix (ECM), which may facilitate the disruption of the ECM barrier before the administration of therapeutics, thereby enhancing their efficacy [125]. This review presents several nanotherapeutics and techniques, including nanoparticles and macromolecules aimed at degrading collagen and hyaluronan in the extracellular matrix, as well as caffeine and modified viruses, alongside the implementation of therapies [126]. Additionally, the impacts of heat, light, and ultrasonic irradiation that ablate extracellular matrix on the distribution and therapy of nanoparticles and cells are also considered. This review aims to elucidate the targeting of ECM in nanotherapeutics, hence advancing cancer therapy [127]. Nonetheless, it presents a novel opportunity to adapt these released tools to focus on other ECM components characterized by low collagen expression, transport systems within the ECM that facilitate more efficient nanoparticle delivery, and reduced half-lives in the body, in addition to improving ligand-receptor mediated cellular uptake of nanoparticles [128].

6.1.2. Targeting hypoxia and acidosis

Tumor hypoxia refers to the state of diminished molecular oxygen availability in bodily tissues. The phenomenon is propelled by augmented tissue bulk and modifications in tumor vasculature, creating an oxygen concentration gradient from established blood arteries to hypoxic areas [129]. Hypoxic cancers exhibit significant metastatic potential and demonstrate resistance to both chemotherapy and radiation. Hypoxia diminishes the effectiveness of chemotherapy as numerous cytotoxic agents rely on oxygen and produce reactive oxygen species, whereas hypoxia obstructs the generation of these species, resulting in decreased apoptosis during treatment [130].

Tumor-associated acidosis can be explained more simply as the buildup of excess acids in the tumor microenvironment (TME), largely due to increased glucose uptake and glycolysis (Warburg effect). This acidic environment reduces the efficacy of many chemotherapeutic

drugs by altering drug uptake and stability, while simultaneously giving tumor cells a survival advantage [131]. In particular, acidosis can make cancer cells resistant to cytotoxic agents, but does not significantly affect cytostatic drugs [132]. Mechanisms proposed include the activation of acid-sensing ion channels, H^+-ATPases, and Na^+/H^+ transporters, which help cancer cells adapt to low pH. Thus, tumor acidity not only drives drug resistance but also contributes to overall tumor progression. Importantly, strategies aimed at neutralizing acidity or buffering the TME have shown some promise, although clinical outcomes remain inconsistent [133].

6.1.3. *Avoiding neovascularization—targeting endothelial cells and pericytes*

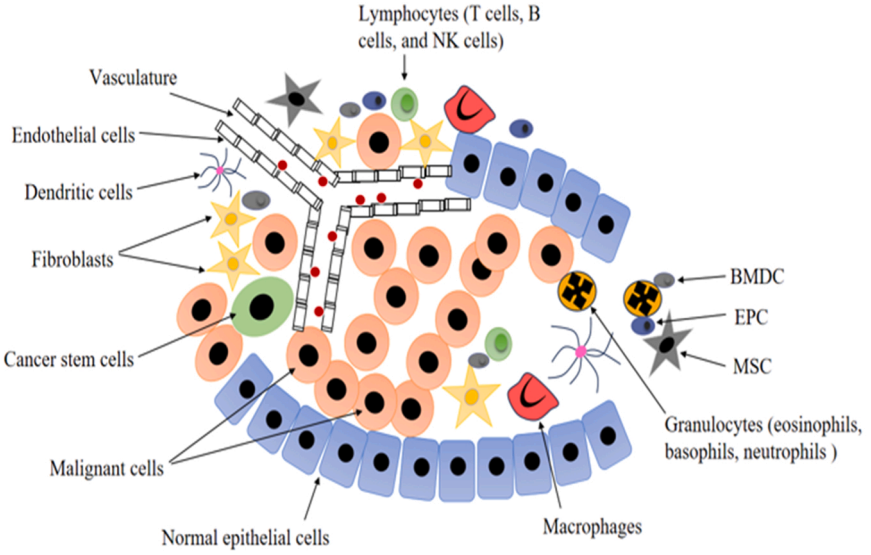
Vascular endothelial growth factor is released by hypoxic solid tumor cells to promote angiogenic sprouting of endothelial cells from existing blood vessels, hence supporting tumor growth [134]. The resolution to this issue has been straightforward: suppress the angiogenic signal of the initiation sequence and, if feasible, promote a reduction in blood supply—although implementing the idea has proven to be challenging. A distinction can be made between normal neovascularization, which should be supported, and pathological neovascularization [135]. The former primarily occurs in the ovaries and uterus, while the involvement of endothelial cells in atherosclerotic lesions represents a notable exception. Consequently, it was reasonable that a treatment strategy to impede neovascularization entailed the pursuit of a minimally bearable dose of a substance [136]. Upon scrutinizing the endothelium of each tumor individually, it becomes evident that each human anti-angiogenic agent, despite varying modes of action on the same target, effectively obliterates the endothelial cells next to the tumor [137].

However, while anti-angiogenic therapy offers the potential to starve tumors by cutting off their blood supply, it also introduces a critical therapeutic dilemma: efficacy versus safety. The same agents that restrict tumor vascularization may also damage normal vasculature, leading to toxic effects in organs such as the liver and kidneys at subtherapeutic doses [138]. Moreover, prolonged suppression of angiogenesis can impair endothelial repair capacity, for instance after radiotherapy, compounding toxicity risks [139]. This highlights the central dilemma: therapies must inhibit pathological tumor angiogenesis while preserving normal vascular functions. All drugs in development are predicated on a continuum action mode as a therapeutic concept: light stimulation does not facilitate revascularization, while severe disturbances lead to tumor regression; these phenomena are observed exclusively in individuals in good health [140].

6.1.4. *Targeting immune system*

Malignant diseases exhibit host immunity suppression, facilitating cancer progression in the absence of effective immunosurveillance [141]. Tumors are encircled by immunosuppressive cell types, including regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages, which facilitate immune evasion and undermine antitumoral responses. Macrophages represent promising targets for elimination through cancer immunotherapy [142]. Tumor-associated macrophages may constitute as much as 50 % of the tumor mass in advanced stages, transitioning from M1 to M2 phenotypes, which leads to immunosuppression and facilitates tumor growth, invasion, and metastasis [143]. As short overview mentioned below in Figure. 3.

Myeloid cells in the TME play a role in immune suppression, particularly through the well-documented ability of myeloid-derived suppressor cells to significantly inhibit T cell proliferation [144]. To address this limitation, myeloid-derived suppressor cells have been targeted to enhance immune system activation in cancer while also mitigating the tumor-supporting functions of these cells [145]. This can be accomplished by inhibiting differentiation and expansion or by reversing their activity and reprogramming them from suppressors to functional antigen-presenting cells. In patients with plasmacytoid dendritic cells, the emphasis on the TME is diminished relative to healthy donors; however, with appropriate education, these cells may serve as an adjuvant in immunotherapy [146]. While data regarding the myeloid population in acute myeloid leukemia treated with DNA methyltransferase inhibitors and/or histone deacetylase inhibitors have been reported, there is limited knowledge concerning the TME in chronic lymphocytic leukemia [147]. Data exist regarding myeloid-derived suppressor cells that secrete IL-8; however, an optimal strategy for targeting these cells remains to be established. The role of these cells in solid tumors, as well as in patients and both mature and immature myeloid cells, remains unclear. There is a lack of data regarding the



Tumor cells are encircled by normal epithelial cells, mesenchymal stem cells (MSC), endothelial progenitor cells (EPCs), and different bone marrow-derived cells (BMDC) in the original tumor microenvironment. The presence of diverse cells within the tumor microenvironment, along with their released soluble substance, signaling molecules, extracellular matrix, and mechanical stimuli, encourages neoplastic changes and supports tumor development and invasion

Fig. 3. The TME fosters neoplastic changes and invasion through interactions with surrounding epithelial, mesenchymal, endothelial, and bone marrow-derived cells.

success of active and adoptive immunotherapy strategies in relation to the repertoire of functional myeloid-derived suppressor cells present in the tumors of patients, indicating a need for validation studies [148].

7. Delivery strategies for nanotherapeutics

Effective cancer therapy is often hindered by the unique barriers posed by the tumor microenvironment (TME). Abnormal vasculature, high interstitial fluid pressure, dense extracellular matrix, hypoxia, and the presence of immunosuppressive cells collectively limit drug penetration and reduce therapeutic efficacy. Therefore, overcoming these barriers is crucial for the success of nanotherapeutics. Smart and multifunctional delivery platforms that can simultaneously navigate TME heterogeneity, enhance tumor selectivity, and minimize systemic toxicity have emerged as the cornerstone of next-generation cancer nanomedicine. Throughout the years, numerous delivery systems have been created for the precise administration of therapeutic and diagnostic substances to cancer cells, thereby reducing the likelihood of systemic drug toxicity [149]. Nanomaterials exhibiting distinctive physical and chemical characteristics, including elevated drug-loading capacity, the ability to precisely modulate drug release rates, and preferential accumulation at tumor sites through the enhanced permeability and retention effect, are especially promising for cancer treatment [150]. The hydrophobic-hydrophilic characteristics of nanomaterial surfaces facilitate the binding of functional moieties that can target certain cancer cell types and TME. Nanotherapeutics utilizing several nanomaterial platforms, including liposomes, inorganic nanoparticles, polymers, dendrimers, and peptide-based nanoparticles, have commenced clinical studies and are demonstrating encouraging outcomes with positive safety profiles in ongoing clinical advancements [13]. This chapter delineates the TME and the strategy of targeting it in cancer therapy, thereafter discussing conventional and cutting-edge enhanced delivery methods for therapies within the TME. The present situation of therapeutically accessible nanotherapeutics is revised [151]. The Novel approaches to regulated drug release and drug delivery include stimulus-responsive nanopreparations is mentioned below in Fig. 4.

8. Passive targeting strategies

Nanotherapeutics that are passively targeted tend to accumulate in TME's due to their size and variable long circulation half-life. This leads to increased local drug exposure while avoiding systemic toxicities and healthy tissue [152].This phenomenon, known as the Enhanced Permeability and Retention (EPR) effect, refers to the preferential accumulation of nanoparticles in tumors compared to normal tissues. It arises because tumor blood vessels are abnormally leaky, allowing nanoparticles to extravasate more easily, while the poorly developed lymphatic drainage in tumors prevents their efficient clearance. Together, these abnormalities create a "trapping" effect, enabling higher local drug concentrations at tumor sites [153]. The tumor vasculature's

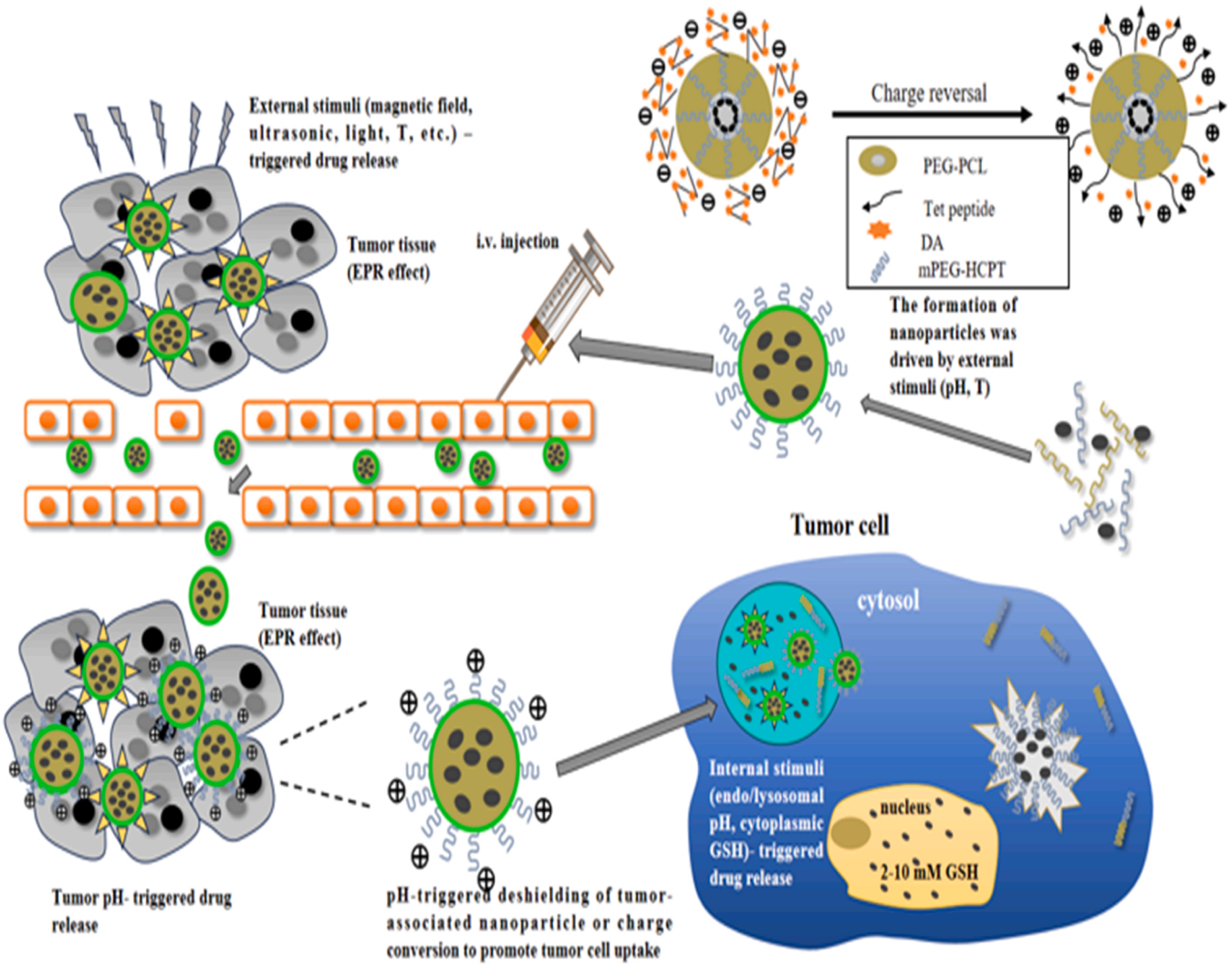


Figure. 4. Novel approaches to regulated drug release and drug delivery include stimulus-responsive nano-preparations.

exceptional permeability and disordered shape, along with insufficient and misaligned lymphatic drainage and ineffective phagocytosis for big molecule and particle clearance, are the driving forces behind the increased permeability and retention effect [153]. Passive targeting can be further optimized by taking advantage of unfavorable biophysiological features of the TME, such as acidic pH, which aids in the dissociation and clearance of surface-attached and entrapped cargo, or by releasing ultralow doses of loaded therapeutic agents triggered by local near-infrared illumination [154]. This approach takes advantage of the increased permeability and retention effect during tumor extravasation. Nanotherapeutic uptake and perfusion are topics of ongoing debate in the field, yet tumors exhibit substantial intratumoral and intertumoral variation. To summarize, passive targeting methods provide a sophisticated and generally efficient way to concentrate therapeutic drugs in a tumor while limiting harm to healthy tissue, but they do have significant limits [73].

8.1. Active targeting strategies

The primary goal of active targeting techniques is to improve nanoparticle accumulation at tumor sites. This happens when the nanoparticles can identify and attach themselves to the receptors that are either produced by the target cells or overexpressed on those cells [155]. On the other hand, stimuli-responsive nanoparticle design for targeted drug release is another definition of active targeting. Several receptor targets that are overexpressed on cancer cells have been identified thus far [155]. Overexpressed antigens on cancer cells, molecules on tumor vasculature and other tumor parenchymal cells, and TME factors on cells around the tumor all fall under this category [156]. The careful selection of molecular targets is a critical determinant of therapeutic success. Effective targets should be abundantly and consistently expressed on tumor cells (or their microenvironment), but absent or minimally present on healthy tissues. Failure to select highly specific targets may lead to reduced therapeutic efficacy, systemic toxicity, or resistance development. One of the most important criteria for creating effective anti-tumor medications is active targeting, which allows for safer, more efficient, and more selective drug delivery to tumor tissue [157].

One potential approach to improving the concentration of nanoparticles in tumor tissue while developing cancer treatments is to modify them with antibodies that target tumor cells [158]. But picking the right tumor cell-specific antigens is crucial to the success of therapy. Either the tumor surface or the tumor matrix can be used to pick a subset of molecules. Anticancer drug concentration in tumor tissues is enhanced by specific antibody-labeled nanoplatforms, whereas the level of anticancer drug in normal tissues is significantly decreased [159]. Furthermore, fluorescence-labeled particular probes function very well for tumor marginal detection or localization of tiny tumors. But there are certain restrictions when using antibodies, particularly monoclonal antibodies: they aren't very stable in physiological settings, they don't penetrate tumor matrices very quickly, and they can trigger undesirable immune reaction attacks [160]. Moreover, heterogeneity in antigen expression across tumor types—and even within the same tumor—can compromise targeting precision. So far, binding proteins have served specialized goals by mimicking the actions of monoclonal antibodies; however, additional research is required to determine whether or not they can enhance tumor penetration, decrease unfavorable immune response, and improve stability in physiological settings [161]. When applied to cell membranes, the monoclonal antibody fails to differentiate between protein-expressing and non-expressing cells. This is why it's crucial to utilize high-quality monoclonal antibodies and validate the protein quantity thoroughly before usage. These procedures are expensive and take a long time [162].

8.2. Stimuli-responsive

Evidence indicates that prioritizing the TME can enhance cancer treatment outcomes. We contend that spatiotemporally active treatments utilizing highly responsive drug carriers, known as nanotherapeutics, and grounded in a thorough understanding of the spatiotemporal and mechanistic complexities of the TME will have significant implications [163]. In practice, these would respond to the complex and dynamic characteristics of the TME, which includes both cellular and non-cellular elements. The TME is influenced by changes such as nutrient deprivation, variable tumor pH, and nestin overexpression [164]. To address this, stimuli-responsive nanotherapeutics have been developed that exploit endogenous and exogenous triggers to achieve precise spatiotemporal drug release. Among the most widely studied endogenous stimuli, tumor acidity provides a practical trigger: nanocarriers designed with pH-sensitive linkages remain stable in the physiological environment (pH 7.2–7.4) but release drugs preferentially in the acidic tumor milieu (pH 6.5–6.8), thereby reducing systemic toxicity. Similarly, enzyme-responsive systems utilize the overexpression of proteolytic enzymes such as matrix metalloproteinases, cathepsins, and hyaluronidases in the TME to selectively degrade nanocarriers, enabling deeper penetration through the tumor stroma.In addition to these intrinsic cues, exogenous stimuli also play a critical role in improving therapeutic control. Thermo-responsive nanocarriers can be triggered by localized hyperthermia (40–43 °C) induced via focused ultrasound or magnetic nanoparticles, as exemplified by temperature-sensitive liposomes like ThermoDox®. Likewise, light-responsive platforms—particularly those activated by near-infrared irradiation—allow on-demand drug release or combined photothermal/photodynamic effects, though their use remains constrained by tissue penetration limits. Another promising approach leverages the redox imbalance of cancer cells, where elevated intracellular glutathione concentrations promote cleavage of disulfide bonds in nanocarriers, leading to selective intracellular release of therapeutic agents.

By clearly defining these stimuli—pH, enzymatic activity, temperature, light, and redox gradients—and emphasizing their practical applicability, it becomes evident that stimuli-responsive strategies greatly enhance the selectivity, efficacy, and safety of cancer nanotherapeutics. Importantly, these approaches are versatile and adaptable across diverse therapeutic cargos, ranging from small molecules to growth factors and RNA-based drugs. This aligns with the broader concept of nanotheranostics, wherein nanostructured platforms are specifically engineered to achieve both diagnostic and therapeutic functions within the TME [165].

The development of a unifying concept for a nanotherapeutic capable of AIGT involves three independent modules. These modules are intrinsic to the nanotherapeutic and must be designed and selected to function synergistically [52].The stems providing context for each module are: Targeting the TME: Nanotherapeutics aimed at the TME without directly targeting tumor cells are anticipated to enhance the efficacy of existing chemotherapy agents, which are presently toxic at the doses required for effective treatment [166]. Nanotherapies aimed at the TME must effectively interact with the pathological TME, which subtly limits the effectiveness of chemotherapeutic treatments, to enhance both current and future cancer therapies [47]. Nanotherapeutics must effectively penetrate the tumor stroma to access both the cancer cells and their TME. The histological architecture of tumor stroma leads to an elevation in interstitial pressure, thereby obstructing the transport of molecules within the extracellular matrix [70]. The residency time of a molecule in the extracellular matrix and its intratumoral diffusion typically depend on physicochemical characteristics, including size and charge, which can inform the optimization of nanomedicines [167].

8.3. Intracellular delivery

Polymers, being negatively charged materials, have excellent gene complex capacity and stability, making them suitable for efficient intracellular gene delivery [168]. These materials can interact with genes to produce nanoparticles, exhibit excellent blood compatibility, and evade elimination by the reticuloendothelial system, facilitating precise accumulation of genes at the targeted tissue or cell [169]. Chitosan is a conventional polymer that demonstrates significant success in gene therapy and exhibits excellent biocompatibility. Polylactic acid is a widely utilized biodegradable polymer, whereas polyethylene glycol is a typically employed surface-modifying agent that enhances material stability and extends blood preservation duration [170]. These biodegradable and biocompatible materials have demonstrated favorable gene therapy results, indicating significant promise for further advancement in clinical applications. Cell-penetrating peptides or analogous small molecule materials with comparable transmembrane transport capabilities operate via an endocytosis-independent mechanism, concurrently inducing membrane hole formation or modifying membrane structures [171]. Cell-penetrating peptides have been integrated with RNA liposomes, fluorophores, magnetic materials, and photosensitizers, demonstrating substantial transmembrane or circulatory efficacy. Overexpressed on the cell surface, promising targets may serve as the foundation for these cell-penetrating drug delivery systems. The integration of targeted pharmaceuticals with cell-penetrating agents represents an alternative avenue for therapeutic development [172].

One of the major challenges of intracellular delivery lies in efficiently transporting therapeutic cargos beyond endosomal entrapment into the cytoplasm or, in some cases, into the nucleus where gene expression machinery resides. Endosomal degradation and limited nuclear penetration significantly reduce therapeutic efficacy. Polymer-based systems address these barriers by enabling endosomal escape through mechanisms such as the “proton sponge effect” (seen with polyethylenimine), pH-responsive swelling, or membrane-disruptive interactions. Additionally, polymers can be engineered with nuclear localization signals or biodegradable linkers that facilitate controlled release directly in the cytoplasmic or nuclear environment, thereby enhancing intracellular bioavailability and therapeutic outcome [171,172].

8.4. Multi-functional nanocarriers

In recent decades, nanoparticles have attracted interest in medication delivery owing to their distinctive characteristics and capacity for targeted administration [173]. Nanoparticles can provide effective answers to the common obstacles of chemotherapy, namely addressing the problems of non-specific targeting and limited drug accumulation in tumors, which are typically associated with conventional systemic chemotherapy [174]. The utilization of nanoparticles facilitates their engagement at the cellular or tissue level, with targeting typically involving the conjugation of targeting ligands to a nanoparticle, thereby enabling interaction with receptors or cell-surface molecules that are overexpressed in malignant tissues [175]. Historically, this method was the primary emphasis for nanoparticle researchers, who engineered targeted nanocarriers to maximize drug accumulation in cancer cells for improved cytotoxicity.

More recently, the focus has shifted toward designing multifunctional nanocarriers that combine several therapeutic and diagnostic capabilities within a single platform. For instance, nanoparticles can be engineered to simultaneously achieve active targeting of tumor cells or stromal elements, incorporate controlled or stimuli-responsive drug release systems, and integrate imaging agents for real-time monitoring. This multifunctional design offers a synergistic advantage enhancing drug efficacy, overcoming stromal resistance, and allowing clinicians to track therapeutic outcomes. Examples include theranostic liposomes conjugated with ligands and imaging probes, quantum-dot based nanocarriers for combined delivery and fluorescence tracking, and iron oxide nanoparticles that serve as both drug carriers and MRI contrast agents. Nevertheless, emerging generations of nanoparticles that specifically target the adjacent stromal environment the non-malignant cells within and around a tumor are advancing as viable alternatives for creating not only multifunctional but also safe, acceptable, and effective nanocarriers [176].

Fibroblasts are of interest due to their involvement in chemotherapy. These are the predominant stromal cells present in connective tissue, facilitating a milieu for angiogenesis that would not transpire otherwise [177]. Every cell type, including cancer cells, stromal cells, and immune cells within the TME, possesses a distinct secreted signature that influences chemotherapy response via its growth factors and cytokines. In the TME, fibroblasts have been demonstrated to obstruct medication penetration [178]. Fibroblastic cells enhance the resistance of cancer cells to cytotoxic agents by the production of soluble substances and direct interaction. Growth factor receptors constitute a class of cell surface receptors that interact with several growth factors and are currently being assessed as potential therapeutic targets [179]. The HER/ErbB receptor family comprises four distinct epidermal growth factor receptors and fibroblast growth factors. Pharmaceuticals targeting these receptors are available. Nonetheless, medication resistance via the stroma remains a significant concern, and mitigating this resistance poses considerable challenges [180].

9. Hybrid nanocarriers

Inorganic metal-based nanoparticles, particularly noble nanoparticles such as gold and silver nanostructures, exhibit unique physiochemical properties, especially in non-linear dimensions [181]. The properties facilitate the development of modern nanocarriers, designed heterogeneously for enhanced anticancer drug delivery and photothermal therapy, achieving significant photothermal conversion effects. Hybrid nanocarrier platforms, nanoparticle bioconjugates, and nanoassemblies that utilize size-tunable photothermal conversion properties have been effectively integrated into inorganic metallic nanoparticles for chemophotothermal therapy [182]. These particles can visualize tumors and penetrate the parenchymal tissue, effectively targeting the tumor. Ongoing research aims to identify optimal combinations of targeting and imaging agents.

The modification of metal, polymer, or liposome-based nanostructures through versatile surface chemistry, either independently or by combining liposomes with metal and mixing polymer with lipid amphiphilic block copolymers, has been extensively utilized [183]. Gold nanostructures conjugated with modified ovalbumin were developed to improve dendritic cell maturation in dendritic cells for cancer therapy. The restricted blood vessel formation in tumors and their unique ability to produce acid present considerable challenges for this design [184]. The integration of graphene oxide or alternative nanoparticles into biocompatible and biodegradable pH-sensitive and stimuli-responsive prodrug nanoparticles facilitates a strategy that is activated by remote triggering and the TMEt [185]. This multifunctional nanoplatform, activated by the TME, was assembled through hydrophobic interaction, subsequently loaded with doxorubicin, and encapsulated with the prodrug. The co-assembled nanoparticles utilized in our photothermal therapy demonstrated effective photothermal conversion and the ability to controllably release drugs in response to unfavorable tumor intracellular pH levels [186].

10. Exosome-based delivery

Exosome-mediated delivery utilizes these natural nanocarriers to transport many therapeutic agents, including small compounds, siRNAs, and miRNAs [187]. Exosomes are particularly advantageous for the targeted delivery of nucleic acid therapies to recipient cells. The ability of exosomes to transport RNA payload to destination cells is facilitated by the several processes via which recipient cells can internalize

exosomes [188]. Certain exosomes, by actively interacting with lipid rafts on the cellular membrane, lower the energy barrier associated with the recipient cell's facilitated endocytosis of the exosomes [189]. Moreover, several exosome types possess proteins that can augment exosome uptake into recipient cells through either clathrin-dependent or caveolin-dependent endocytosis. Exosomes are a minimally invasive approach to systematically alter an adverse TME, facilitating the efficacy of additional therapeutic medicines against the disease [190]. The utilization of exosomes is pragmatic and can be more easily incorporated into clinical practice owing to the expedited regulatory approval procedure for therapies comprising natural biolipid particles, in contrast to synthetic non-lipid nanoparticles. Because exosomes are naturally derived, they demonstrate superior biocompatibility and reduced immunogenicity compared to many synthetic nanocarriers. Unlike liposomes or polymeric nanoparticles, which may trigger complement activation or immune recognition, exosomes exhibit intrinsic immune tolerance, thereby offering a safer delivery profile in vivo. Exosomes serve as delivery vehicles beyond merely changing the TME. Given that exosomes participate in pathways that sustain or alter nearly all organ systems, exosome-mediated delivery holds promise for therapeutic effectiveness beyond oncology [191]. The advancement of exosome-based delivery holds significant potential for enhancing our comprehension of exosome biology. To advance exosomes as effective cancer therapies, it is essential to identify exosomal surface markers and enhance the understanding of the cell type-specific packaging of exosomal populations. Only then will we be able to detect, categorize, and encapsulate cancer-modulating exosome populations [192].

10.1. Combination therapy delivery

Nanoparticles can combine numerous therapeutic cargoes into a single structure due to their advanced manufacturing capabilities. Hydrophilic macromolecules, peptides, nucleic acids, antibodies, and tiny hydrophobic compounds all fall within this category [193]. This is a huge boon when it comes to effectively mixing medications that have synergistic effects to boost treatment efficacy and counteract drug resistance. A combination therapy delivery system that is easy to administer is achieved by accurately controlling the spatial arrangement of these in the nanoparticle [194]. This arrangement determines both the release kinetics and their position within the delivery site. Responsively releasing nanoparticle delivery and actively targeting ligand conjugated. Reducing interstitial hypertension, enhancing drug penetrability, restricting angiogenesis, enabling hypoxia, upregulating drug efflux pumps, and weakening tumor cell membranes are therapeutically desirable cancer characteristics that impact solid tumor fate [195]. In addition to allowing for the actual killing of cancer cells, uniform distribution of the drug throughout the tumor also leads to more consistently controlled drug concentrations in cancer cells. On the other hand, conventional free drugs have limited success in targeting and penetrating cancer cells due to the complicated and diverse TME [28]. Clinically, the rationale for nanoparticle-enabled combination therapy lies in its ability to simultaneously address multiple hallmarks of cancer, thereby reducing the likelihood of therapeutic resistance and enhancing overall efficacy. Several FDA-approved nanomedicines, such as Vyxeos® (a liposomal co-formulation of daunorubicin and cytarabine for acute myeloid leukemia), have already demonstrated the superiority of combination delivery over single-drug formulations. These clinical successes underscore the translational relevance of nanoparticle-based combination therapy, highlighting its potential to improve patient survival, minimize relapse, and offer more durable treatment responses in oncology. A smart medication delivery platform based on nanoparticles has recently been developed to circumvent these delivery obstacles, thanks to recent advancements in nanotechnology. The most important developments can be boiled down to two separate functional criteria: actively targeting ligand coupled and responsively releasing nanoparticle delivery [196].

11. Preclinical and clinical studies of nanotherapeutics

The efficacy and potential of addressing the TME through nanoparticle design have resulted in an increase in preclinical investigations and clinical trials focused on utilizing nanotherapeutics to restructure tumors for enhanced delivery of other anticancer therapies [166]. These effects encompass the control of the immunological phenotype of myeloid and/or immune cells, the normalization of blood vessel physiology and function, and the regulation of the extracellular matrix. We present many instances of targeting nanoparticles for the TME to re-engineer it and examine the impact of such modification on other anticancer therapies [197]. We categorize these research according to the distinct cell types they address, such as endothelium normalization through antivascular treatment administration and enhancement of T cell infiltration by altering the expression of tumor and stromal cells. With over 60 nanotherapeutics at various stages of clinical development and several in late-phase studies, the sector is positioned to provide a more efficacious nanomedicine [198].

The future of cancer nanotherapeutics lies in employing nanoparticles for the targeted modulation of the TME and in combination therapies to enhance treatment efficacy beyond the capabilities of nanocarriers acting independently or merely delivering therapeutic agents [199]. Research on particle designs aimed at modifying the microenvironment for enhanced and prolonged delivery of agents functioning through specified mechanisms of action includes immune-regulating, immune-priming, and immune-activating agents that would reprogram various subsets of innate effectors and natural killer cells. Furthermore, irrespective of delivery platforms, targeted strategies addressing certain characteristics of the TME may be necessary for achieving optimal therapeutic efficacy. It is clear from vast literature that the study and design of nanotherapeutics involve surrogate markers of therapy efficacy, such as immune-cell infiltration [200]. An overview of nanotherapeutics in clinical trials targeting the TME are enlisted below in the Table 2.

11.1. Key findings from preclinical studies

Recent publications from several preclinical investigations, many involving clinically licensed nanocarriers, indicate that nanotherapeutic strategies may significantly enhance the treatment of some of the most formidable tumors of our era [201]. A primary source of enthusiasm for developing nanotechnology lies not only in its potential utility for certain cancer subtypes but also in its capacity to enhance the treatment of many histological cancer types. This holds true for both cell-based and antibody-based techniques aimed at modulating the TME, as well as for the wider range of therapeutic drugs that may be co-delivered alongside these payload categories [202]. The second wave of nanomedical interventions is already emerging, aiming to target the TME. After more than ten years of preclinical and clinical study, it is established that molecularly designed nanoparticles may target and infiltrate the interior milieu of solid tumor masses. The capacity to successfully penetrate the physical and biochemical barriers of the TME is a fundamental characteristic of emerging cancer nanomedicine and serves as a basis for the development of enhanced nanotherapeutic techniques in the future [203]. Nonetheless, the predominant—indeed, overwhelming—focus of nanotherapy research has been on targeting cellular constituents of solid tumors, aiming to directly disrupt essential connections required for cancer cell proliferation, a strategy that has thus far demonstrated efficacy primarily against a restricted subset of highly inflammatory solid tumors [204].

11.2. Clinical trials of nanotherapeutics

Both SPi-077 and ombrabulin liposome, which aim at targeting tumor-associated macrophages (TAMs), have successfully concluded Phase I clinical trials. CRLX101, NRX194204, BNC105P, BMS-986253,

Table 2
Detailed Analysis of Therapeutic Agents: Target Sites, Mechanisms of Action, Bio-availability, and Cancer Types.

S.N.	Therapeutic agent	Target site	Mechanism of action	Bioavailability	Cancer type	Reference
1	LY01008 and Bevacizumab	Anti-VEGF antibody	Bind to VEGF, inhibit its binding to vascular endothelial cell surface receptor, and inhibit tumor angiogenesis	111.4 %	Non-small cell lung cancer	[80]
2	Sunitinib and Sorafenib	c-KIT inhibitor	By focusing on the RAF and VEGFR intracellular tyrosine kinase domain, sorafenib and sunitinib reduce angiogenesis and stop blood vessels from growing.	40–50 % Oral	Renal cell	[81]
3	Pazopanib (Votrient)	Tyrosine kinase Inhibitor	The inhibition of the intracellular tyrosine of VEGF receptor (VEGFR) and PDGF receptor (PDGFR) are responsible for its antiangiogenic properties.	14–39 % Oral	Renal cell	[82]
4	Bevacizumab (Avastin)	Inactivate serum VEGF	By selectively attaching to circulating VEGF, the binding of VEGF to its cell surface receptors is inhibited.	100 % (IV only)	Colorectal cancer	[83,84]
5	Everolimus (RAD001)	mTOR inhibitor	mTOR inhibitor has strong binding affinity to FK506 binding protein−12 (FKBP−12)	16 % Orally	Renal cell	[85]
6	Apatinib	VEGFR2	Inhibits VEGF-mediated endothelial cell migration and proliferation thus blocking new blood vessel formation in tumor tissue	100 % when administered with food	Gastric cancer	[86]
7	Lenvatinib	VEGRF, FGFR, PDGFR α-β	Multiple receptor tyrosine kinase, Block receptors are required for tumor growth and blood vessel	85 % Oral	Thyroid cancer	[87]
8	Digoxin	Cardiovascular system	Attaches to and blocks the sodium/potassium-ATPase (sodium pump) in the plasma membrane of heart muscle cells.	50–90 % (oral dose)	Prostate cancer	[88]
9	Acetazolamide	Proximal tubules	Increasing the pH of the urine and releasing bicarbonate in urine	70–90 % Oral	Bladder cancer	[89]
10	Gemcitabine	C-site of RR1	Substituting the foundational units of nucleic acids while DNA extends, halting the advancement of tumors, and encouraging the death of cancerous cells.	10 % Oral	Non-small cell lung cancer, pancreatic cancer	[90]
11	Rapamycin	mTOR	Inhibits the serine/threonine protein kinase that affects the phosphorylation state of mTOR	14 % oral	Renal cancer	[91]
12	Cediranib	VEGF-A inhibitor	By obstructing the VEGF receptors, cediranib restricts the formation of new blood vessels necessary for supporting tumor expansion.		Ovarian cancer	[92]
13	Ramucirumab	Anti-VEGFR	Inhibiting VEGF-induced receptor phosphorylation can stop the permeability, proliferation, and migration of endothelial cells of human triggered by ligands.	100 % IV	Gastric adenocarcinoma	[93]
14	Emactuzumab	CSF−1R	Preventing both the function of the influx of TAMs into the tumor microenvironment and CSF1R-driven tumor-associated macrophages (TAMs).	-	Squamous cell carcinoma	[94]
15	Chiauranib	Tyrosine kinase inhibitor	Inhibitor that targets multiple kinases, including those involved in angiogenesis, mitosis (aurora B), and chronic inflammation (CSF−1R)	-	Ovarian cancer, small cell lung cancer	[95]
16	Sitravatinib	c-Met, VEGFD, TRK	Attaches to and blocks the function of various RTKs such as growth factor receptor, hepatocyte, mast/stem cell growth factor receptor, tyrosine-protein kinase receptor blocks the signal transduction pathway controlled by these RTKs, and decreases the growth of tumor cells.	-	Renal cancer cell	[96]

and CRLX301 are novel nanomedicines that target endothelial cells, disulfide isomerase, hypoxia-inducible factor 1-alpha, and CCL2, and have successfully completed Phase I clinical studies. These medicines have demonstrated pharmacodynamic biomarkers in the management of advanced solid malignancies [205]. Nonetheless, to date, none have been validated for their efficacy or therapeutic benefit, suggesting that the clinical advancement of TME-targeting nanomedicines remains in its nascent phase. This imbalance between the large number of Phase I studies and the scarcity of Phase II or III trials reflects multiple barriers to clinical translation. Scientifically, preclinical models often fail to fully mimic the complexity of the human TME, while pharmacokinetic and biodistribution challenges, along with long-term toxicity concerns, limit progress. Economically, large-scale and reproducible manufacturing of nanotherapeutics is both costly and technically demanding. Regulatory agencies also impose stringent requirements for safety, stability, and quality, which are more difficult to satisfy for complex nanosystems compared to conventional drugs. Together, these factors explain the translational bottleneck and highlight the need for standardized evaluation frameworks and improved translational models to accelerate clinical advancement. In addition, patient heterogeneity and the adaptive nature of the TME itself create variability in therapeutic outcomes, making it harder to demonstrate consistent clinical benefit across diverse trial populations. These combined scientific, economic, and regulatory bottlenecks explain why most TME-targeting nanotherapeutics stall after early-phase trials and underscore the urgent need for more predictive preclinical models, standardized manufacturing protocols, and tailored regulatory frameworks.

In summary, tumor-associated macrophages (TAMs) serve as a critical component of the local immune network, acting as a threshold barrier that inhibits the accumulation of therapeutic agents while simultaneously facilitating the evasion and transformation of upstream adaptive immune infiltration within the TME, thereby advancing tumor progression [206]. The increase of M2 macrophages in many human solid tumor types correlates with poorer survival outcomes. The prevailing views on M2 macrophages in immune response and tumorigenesis suggest that, regardless of the most rational theory, the eradication of M2 macrophages is crucial for the enhancement of anti-tumor immunity and the prevention of tumor evasion and recurrence. This book aims to evaluate the advancement of nanotechnology in altering the biological properties of M2 macrophages and to assess the efforts and current state of various nanotherapeutics aimed at M2 macrophages in the development pipeline. The potential applications of M2 macrophage-targeted nanotherapeutic methods in anti-tumor immunity are concurrently examined [207].

12. Challenges and future directions

The altered intracellular trafficking of available drugs and the development of resistance to nanoparticle-based complex formulations are unresolved issues. NP-mediated delivery offers potential therapeutic options; however, safety concerns related to NP usage, uncertainties regarding their pharmacological properties, and difficulties in NP synthesis have hindered effective clinical translation [208]. The variability in TME characteristics, including extracellular pH, tissue permeability, hypoxia, and immune suppression, presents challenges in achieving the desired therapeutic efficacy of pre-validated nanotherapeutics across various cancers [209]. The experimental results do not consistently replicate in clinical environments because of the inherent heterogeneity in the intrinsic characteristics of solid tumors and the patient population. Thus, a thorough preclinical evaluation of NP formulations in relevant cancer models is essential to accurately predict clinical treatment outcomes [210].

Nanoparticles effectively surmount numerous biological obstacles to facilitate targeted medication distribution in pre-validated nanotherapeutics. Concerns over the undesirable biological interactions of NPs, ambiguous pharmacology, erroneous synthesis, and significant regulatory obstacles contribute to the translational gap [211]. The intrinsic variability in TME attributes, including tissue permeability, heightened cellular metabolism, hypoxia, immune suppression, and fluctuations in extracellular pH, has presented obstacles in attaining the desired therapeutic efficacy of pre-validated nanotherapeutics across various cancers. The inherent variety in targeting the TME with nanoparticles does not provide universally relevant nanoparticles across different tumor types [47]. Furthermore, the intricacy of liquid biopsy presents obstacles for point-of-care applications utilizing nanoparticles. The medical and ethical implications of utilizing NPs necessitate risk awareness, ongoing toxicity validation, post-treatment evaluation, and the identification of clinically significant tumor targets with innovative therapeutic approaches, thereby promoting the advancement of the nanotherapeutic domain in cancer treatment [212].

13. Challenges in translating nanotherapeutics to clinical practice

Nanotechnology possesses the potential to transform existing therapeutic strategies for cancer treatment. To do this, it is essential to possess a precise comprehension of the specific issues that must be confronted [213]. Numerous effective preclinical investigations with novel nanoparticle formulations and combinations have been conducted; nevertheless, the transition to clinical practice is frequently challenging, and only a limited number of nanoparticle carriers for various cancer types have successfully progressed to clinical trials. A deeper comprehension of the basic mechanisms of tumors and the interactions of tumor-endothelial cells, tumor-macrophage cells, and tumor-stromal cells is essential to maximize the potential advantages of nanotherapeutics. Furthermore, funding is a critical factor for future development realistic clinical situations [152]. A persistent limitation is the over-reliance on subcutaneous xenograft models, which fail to replicate the complexity of human tumors. More predictive platforms such as chorioallantoic membrane (CAM) assays, patient-derived xenografts (PDX), immunocompetent syngeneic models, and 3D tumor spheroids offer improved translational accuracy. Incorporating spontaneous tumor models and immune-competent systems can better capture the influence of host–tumor interactions and immune responses, thus enhancing preclinical predictability. Regulatory hurdles also remain a major barrier. Despite promising efficacy and safety data, nanoparticle formulations often face difficulties due to the absence of harmonized regulatory frameworks specifically tailored for nanomedicines. The variability in characterization techniques, long-term toxicity assessment, and quality control makes approval pathways unclear. The majority of research on nanoparticle-based cancer therapies continues to utilize subcutaneous tumor models that lack predictive accuracy. Moreover, tumor therapy is integrated with additional cancer care strategies, potentially resulting in unforeseen synergistic treatment benefits. Governmental assistance via expanded funding initiatives is crucial for maintaining growth in this unique venture. The industry's competitiveness relies on tangible enhancements in clinical treatment outcomes. Inability to fulfill that need will jeopardize this methodology in both academic and industrial contexts [214]. Looking ahead, technological innovations may help overcome existing barriers. Artificial intelligence (AI) and bioinformatics are emerging as powerful tools for the rational design of nanoparticles, enabling in silico prediction of pharmacokinetics, biodistribution, and tumor selectivity. AI-driven platforms also hold promise for developing personalized nanomedicine strategies tailored to individual tumor biology [49]. Another major frontier involves addressing tumor microenvironment (TME) heterogeneity. Future strategies emphasize multifunctional nanoparticles engineered to respond to multiple stimuli (pH, redox, enzyme activity, or hypoxia) simultaneously, ensuring precise, on-demand drug release. These intelligent designs could substantially improve efficacy while minimizing off-target effects.

13.1. Emerging trends in nanotherapeutics research

In cancer therapy, nanotherapeutics the combination of nanotechnology and therapeutics is quickly becoming the norm. Through active and passive targeting to tumors and multidrug delivery, nanotherapeutics have shown tremendous promise in enhancing cancer therapy outcomes [69]. The review's main point is that it zeroes in on the TME as a target for new nanotherapeutics and treatment approaches. Surgery, radiation therapy, and chemotherapy are all part of the conventional cancer treatment arsenal that aims to destroy cancer cells [83]. Although a lot of cancer treatments work to slow the growth of cancer cells at first, they often don't stop tumors from growing back or spreading to other parts of the body, which is why cancer still kills people. This fact, along with the fact that cancer is complex and has many different aspects, highlights the urgent need for innovative new treatments [215]. Consequently, nanotherapeutics and other innovative drug delivery technologies are finding more and more applications in reeducating the TME. Nanotherapeutics have many benefits, such as the capacity to fight drug resistance, targeted distribution, reduced drug-related side effects, and effective and sustained drug delivery. An Underappreciated Tool in the Treatment Toolbox: Nanotherapeutics The significance of nanoparticle size and composition in achieving optimal therapeutic effects has been increasingly acknowledged by drug delivery systems during the past 40 years [216]. Nevertheless, the numerous advancements in nanoparticle design are still not fully utilized by the nanoparticle systems that are now approved. There is a great deal of unrealized potential for safer and more effective nanoparticle cancer therapy, thanks to our expanding knowledge of the pharmacokinetics of cancer drug delivery, an increasing number of nanoparticle compositions that have been thoroughly studied, and a potent array of targeting approaches [217]. Potentially holding the key to treating the disease could be the TME, which includes the tumor vasculature, stromal cells, and the extracellular matrix. Thus, given the intricacy of this dynamic and impactful target, the time is ripe to concentrate on creating nanoparticle therapeutics that can keep up. When it comes to cancer treatment, small molecule medications are still the gold standard [17]. Low tumor selectivity and high hydrophobicity can restrict their performance, causing problems with solubility, pharmacokinetics, off-target effects, and drug resistance. To that end, cancer nanotherapeutics offer a promising new way to target cancer cells with powerful small molecule and biologic medications. Because of their enhanced circulation, targeted drug release, and tumor-specific accumulation, nanotherapeutics show tremendous promise as a cancer treatment [218]. Because it disregards the TME, which is crucial for cancer development, medication resistance, and immune response evasion, conventional cancer treatment, which centers on cancer cell targeting, often fails.

Another therapeutic method with biomimetic characteristics that are TME - targeted take use of the unique cellular and tissue composition of tumors [219]. The use of several nanotherapeutics in cancer treatment has been greenlit, and several have already finished phase III studies with positive results. This review delves into the latest developments in nanotherapeutics research and development, including their possible uses and therapy techniques that target the TME [220,221].

13.2. Regulatory bottlenecks in clinical translation of nanotherapeutics

Nanotherapeutics hold immense promise for improving cancer care, yet their clinical translation remains limited. Beyond scientific and economic barriers, regulatory challenges significantly restrict approval and widespread adoption. Unlike conventional small-molecule drugs, nanomedicines are highly heterogeneous, with therapeutic performance depending on particle size, surface chemistry, and stability, all of which influence pharmacokinetics and biodistribution. These complexities make it difficult to evaluate safety and efficacy using traditional drug approval standards. Current regulatory pathways often rely on guidelines originally designed for biologics or conventional pharmaceuticals, which do not fully capture the unique behavior of nanosystems. As a result, agencies typically require extensive preclinical data, long-term toxicity studies, and stringent quality control, leading to delays, high costs, and limited progression of promising candidates.

There is increasing recognition of the need for specific regulatory frameworks for nanomedicine. Dedicated guidelines that standardize nanoparticle characterization, establish quality-by-design principles for manufacturing, and address long-term safety monitoring could streamline approval processes. Moreover, harmonized international standards would reduce variability between agencies and accelerate global development. Establishing such frameworks will be critical to moving beyond early-phase trials and ensuring that clinically effective nanotherapies reach patients.

Looking ahead, artificial intelligence (AI), machine learning, and bioinformatics could play a pivotal role in overcoming some of these bottlenecks. By integrating large datasets on nanoparticle physicochemical properties, tumor genomics, and clinical outcomes, AI-driven models may guide the rational design of nanoparticles with optimized targeting, safety, and therapeutic efficacy. Similarly, bioinformatics tools enable patient stratification and personalized nanomedicine approaches, aligning regulatory evaluation with precision medicine strategies. Incorporating these digital tools into regulatory science has the potential to accelerate approval processes and support the safe, efficient translation of nanotherapeutics into clinical practice.

14. Conclusion

Significantly, obstacles persist in the advancement of nanotherapeutics aimed at the TME. These challenges encompass targeting efficacy and harm to nontumor tissues. Emphasis may be directed towards the development of TME-responsive materials that can release therapeutic drugs exclusively within the TME, as well as enhancing the specificity of active targeting techniques. Our growing comprehension of the intricate interactions and reciprocal regulation between cancer cells and stromal cells within the TME is anticipated to expedite the TME-specific functions of these materials and improve the precision of cancer therapies. Therefore, we anticipate a rise in the clinical applications of the proposed nanotherapeutics in the near future. Our improved comprehension of the processes by which nanotherapeutics exert antitumor effects has significant potential for alternative treatment techniques and will profoundly influence future cancer research. Successful clinical translation of nanotherapeutics in cancer treatment necessitates a complex system that ensures efficient drug delivery to tumors, precise targeting of tumor cells, presentation of specific targeting motifs within the TME, and the mitigation of stroma-induced drug resistance. This study examines nanotherapeutics intended to target various cells within the TME. Nanotherapeutics targeting tumor cells represent a significant focus of research in cancer therapy. The education of present and future researchers and regulatory agencies of the importance of addressing the TME and facilitating its swift clinical application will result in innovative methodologies and enhanced patient care. These factors reinforce our assertion that nanotherapeutics aimed at the TME possess significant potential to transform contemporary cancer treatment. Looking forward, multifunctional nanoparticles capable of responding to multiple stimuli within the heterogeneous TME, such as pH, redox potential, and enzyme activity, offer a promising strategy to overcome intratumoral variability. Such multi-stimuli–responsive platforms, especially when integrated with theranostic functionalities, may enhance therapeutic precision, improve treatment monitoring, and ultimately reduce resistance, thereby shaping the next generation of clinically relevant nanotherapeutics.

CRediT authorship contribution statement

Vetriselvan Subramaniyan: Writing – review & editing, Visualization. **Vishesh K. Maurya:** Writing – original draft, Validation, Investigation. **Pravesh Kumar Sharma:** Visualization, Validation, Investigation, Data curation, Conceptualization. **Nirmal Joshi:** Validation, Conceptualization. **Vishal Bhati:** Writing – review & editing, Writing – original draft, Validation, Resources, Investigation, Data curation, Conceptualization. **Sonima Prasad:** Writing – original draft, Supervision, Conceptualization. **Deepak Joshi:** Writing – original draft, Supervision, Resources, Conceptualization. **Mayuri Bapu Chavan:** Validation, Visualization, Writing – review & editing. **Sumit Durgapal:** Conceptualization, Validation, Visualization, Writing – review & editing. **Madhu Gupta:** Supervision, Conceptualization. **Keshav Paudel:** Supervision, Conceptualization.

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