Proceedings of ICMMGH 2027 Symposium: Clinical OMICS for Drug Discovery and Personalized Medicine
DOI: 10.54254/2753-8818/2027.MB37184

Design and Limitations of Tumor Microenvironment-Responsive Nanocarriers for Targeted Drug Delivery

Xinyu Yang

Dulwich College, Shanghai, China
xinyuyang1010@outlook.com

Abstract. Cancer is still a major cause of death worldwide, and the old ways of treating cancer have defects, such as systemic toxicity, quick drug resistance, and poor targeting. Given the favorable features of the tumour microenvironment, conventional therapy has shown limited efficacy, thus, new nanocarrier-based drug delivery systems are needed. This review will introduce the necessary biological and physical characteristics of the tumour microenvironment and present current responsive nanoparticle platforms, such as lipid-based, polymer-based, inorganic, biological, and hybrid systems, associated with their construction patterns, therapeutic effects, and preclinical progress. Preclinical data show that these nanocarriers improve tumour accumulation and realise controlled, localised drug release. However, clinical translation still faces many problems, such as poor manufacturing feasibility, unstable circulation, extended-term biosafety risks, tumour heterogeneity, and a lack of standardised evaluation systems. Another reason is that the preclinical model may not be in the same environment as a person. The following are some promising directions for this paper: multimodal analysis, optimisation with additional data from artificial intelligence (AI), and descendant models of patients. The above ways can help to solve the problems caused by translation and provide new directions for the development of cancer therapy.

Keywords: Tumor Microenvironment, extracellular matrix, nanoparticles, targeted drug delivery, clinical translation

1. Introduction

Cancer remains one of the most devastating diseases worldwide, accounting for roughly one-fifth of all human deaths. In 2024 alone, there were 20.6 million newly diagnosed cases, and 9.8 million fatalities reported [1]. At the genetic level, cancer develops through the gradual accumulation of somatic gene mutations, which then drive uncontrolled cell growth, invasive behavior, and ultimately distant metastasis through circulatory and lymphatic routes. Traditional clinical treatments—such as surgery, chemotherapy, radiotherapy, and hormonal therapy—can achieve basic control of tumors, but they are still limited in important ways. The remaining tumors are usually too microscopic for surgery to completely remove them, and chemotherapy is also affected and hindered by factors such as multiple drug resistance and as systemic toxicity. At the same time, the existing radiotherapy methods are difficult to precisely target deep lesions, and hormone therapy may also

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2027.MB37184

gradually develop resistance, reducing the quality of patients' lives [2]. More importantly, due to the heterogeneity and genetic differences of tumors, the treatment effects vary from person to person, which greatly limits the application scope of traditional therapies.

The tumor microenvironment (TME) is a biological system with high heterogeneity and complexity, and it occupies a major part in tumor progression, immune evasion, and therapeutic resistance [2]. Unlike normal neutral tissues in the body, the typical characteristics of the TME are a slightly acidic pH value, persistent hypoxia, vascular abnormalities, a remodeled dense extracellular matrix, and immunosuppressive cell components. These unique physicochemical and biological properties not only promote the development of malignant tumors, but also generate multiple biological barriers, preventing conventional anti-cancer drugs from being effectively delivered and exerting their expected effects [3]. Therefore, managing the treatment barriers caused by the TME has become the central focus of modern oncology research.

With the rapid progress of nanobiomedicine, TME-responsive nanocarriers have been regarded as a targeted treatment method with a promising long-term development prospect. Unlike passive targeted nanocarriers, intelligent nanocarriers can respond to endogenous TME signals, such as acidity and hypoxia, in a controllable manner, thereby directly releasing drugs at specific sites. This can not only reduce off-target toxicity but also help improve delivery obstacles related to the TME [2]. The key TME features will be further systematically reviewed, with major responsive nanocarrier platforms being categorized, and their current application progress as well as the restrictions that still limit clinical translation, with the aim of offering theoretical guidance for the development of more precise tumor nanotherapies.

2. Typical characteristics of tumor microenvironment

2.1. Acidic microenvironment

In healthy human tissues, extracellular pH is tightly regulated at about 7.40 ± 0.2 to support normal metabolism and physiological functions. By contrast, nearly all solid tumors create a heterogeneous acidic microenvironment, with extracellular pH typically falling between 6.5 and 7.1, while intracellular tumor pH stays only weakly alkaline [4]. This acidification mainly comes from the Warburg effect, a well-known metabolic hallmark of malignant cells. Regardless of oxygen availability, tumor cells tend to rely on aerobic glycolysis, producing large amounts of lactic acid and hydrogen ions. Because tumor blood vessels drain inefficiently, these byproducts build up in the tumor interstitial space, resulting in persistent local acidification. Tumor acidity is not just a passive metabolic outcome—it actively contributes to malignant progression and therapeutic resistance. Low pH can increase matrix metalloproteinases to break down ECM components, thereby promoting invasion and distant metastasis [4]. It also inhibits the growth and killing ability of anti-tumor T cells and natural killer cells, which further drives an immunosuppressive TME. In chemotherapy, many standard first-line drugs are weak bases, or weakly alkaline, and are likely to become protonated and trapped extracellularly in acidic tumor tissues, which prevents them from exerting sufficient intracellular cytotoxic effects. At the same time, acidic stress can enhance tumor drug efflux pumps, ultimately leading to multidrug resistance.

2.2. Hypoxic microenvironment

Hypoxia is a universal pathological hallmark of solid tumors, caused by an imbalance between uncontrolled tumor cell proliferation and structurally defective tumor angiogenesis [5]. Rapid tumor

DOI: 10.54254/2753-8818/2027.MB37184

growth drastically increases local oxygen consumption, while newly formed tumor vessels feature tortuous morphology, incomplete walls and disordered perfusion, unable to meet oxygen demands and forming persistent hypoxic regions in deep tumor tissues. Hypoxic stress stabilizes hypoxia-inducible factors (HIFs), the core transcription factors that activate hundreds of downstream genes involved in glycolysis, angiogenesis, metastasis and immune suppression [4]. HIF-mediated metabolic reprogramming further accelerates the glycolysis of aerobic sugar and produces more acidic metabolites, ultimately forming a cycle where acidification and hypoxia reinforce each other [5]. From a functional perspective, hypoxia can reduce the sensitivity of slow-cycling tumor cells to radiotherapy and conventional chemotherapy, inhibit the infiltration and activation of anti-tumor immune cells, and prevent universal treatment resistance. Distinct from normal tissues, tumor-specific hypoxia can be seen as a reliable targeted stimulus. Hypoxia-responsive nanocarriers remain stable in normal tissues and can achieve targeted drug activation, releasing exclusively in hypoxic tumor regions, improving therapy accuracy and reducing off-target toxicity.

2.3. Disordered tumor vascular structure

Normal tissues have regular and well-structured blood vessels with stable perfusion, enabling effective material exchange. On the contrary, persistent hypoxia and inflammation can stimulate the remodeling of pathological blood vessels in tumors, forming a vascular network with structural defects and functional disorders [6]. Overexpressed vascular endothelial growth factor (VEGF) in hypoxic tumour areas leads to over-proliferation of endothelial cells, causing tortuous, irregular tumour vessels with incomplete walls and high abnormal permeability [3]. Such abnormal vascular structures create multiple physical obstacles for conventional cancer therapy. Increased interstitial fluid pressure in tumours limits the perfusion and accumulation of circulating small-molecule chemotherapy agents, while leakage of vascularisation results in premature drug washout and insufficient penumbra blood pool in deep tumour tissue [6]. Disordered perfusion also worsens regional hypoxia and acidification, further entrenching a drug-resistant TME. Nanocarriers can bypass these vascular barriers via the enhanced permeability and retention (EPR) effect. Nanoparticles with a size of 10–200 nm can accumulate in tumour tissues preferentially via passive targeting, while modification of particle size, charge, or target ligand on the surface of particles further improves deep tumour penetration, substantially augmenting intratumoural drug accumulation and activity [7, 8].

2.4. Dense extracellular matrix barrier

Traditionally, the normal extracellular matrix (ECM) keeps a loose and dynamic balanced structure to maintain the stability of tissue, whereas, in cancerous tissues, pathological ECM remodelling is irreversible and tumor patients form a dense and highly cross-linked stromal barrier, which seriously restricts drug delivery. ECM densification is principally caused by the CAFs induced by tumor-derived inflammatory factors. Activated CAFs massively produce type I/III collagen and hyaluronic acid, which promote excessive ECM cross-linking, enhance ECM stiffness, and narrow the interstitial diffusion pathway of ECM [3]. Dense ECM serves as a key physical barrier: small-molecule chemotherapeutic drugs only accumulate in the superficial layer of the tumor, fail to penetrate deep tumor tissue, and residual tumor cells are always left, resulting in recurrence and resistance to therapy [9]. Not only does the dense ECM hinder diffusion, but the remodelling ECM squeezes tumor vessels to aggravate tumor hypoxia and acidification, and activates oncogenic signalling pathways to promote tumor growth and metastasis, leading to a self-stabilized malignant

DOI: 10.54254/2753-8818/2027.MB37184

TME feedback loop [9]. TME-responsive nanocarriers effectively break this barrier by loading matrix-degrading components or stimulus-cleavable structures, enabling targeted ECM degradation, opening drug diffusion channels, remodeling the stromal microenvironment, and synergistically enhancing anti-tumor efficacy [8].

2.5. Heterogeneous cellular components of tumor microenvironment

The TME is a heterogeneous interactive system composed of tumor cells, stromal cells, and immune cells, whose complex crosstalk drives tumor progression, immune escape, and therapeutic resistance [2]. Unlike the immune surveillance state of normal tissues, the TME is dominated by immunosuppressive cell subsets that construct a protective barrier for tumor growth. Tumor-associated macrophages (TAMs) are the most abundant immune cells in tumors, predominantly polarizing into pro-tumor M2 phenotypes under tumor cytokine induction [3]. M2-TAMs secrete immunosuppressive cytokines (IL-10, TGF-β) and pro-angiogenic factors, inhibiting CD8+ T cell cytotoxicity, promoting angiogenesis and facilitating tumor invasion. Myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) are also massively enriched in TME, jointly suppressing anti-tumor immune responses [3]. Stromal CAFs further amplify immune suppression by recruiting immunosuppressive cells and remodeling the ECM barrier, while vascular endothelial dysfunction worsens regional hypoxia. The synergistic interaction of these heterogeneous cellular components stabilizes the malignant TME, fundamentally causing the failure of traditional surgery, chemotherapy and immunotherapy [9].

3. Classification and research progress of tumor microenvironment responsive nanocarriers

3.1. Lipid-based nanocarriers

Lipid-based nanocarriers, including liposomes, polymeric micelles and solid lipid nanoparticles, are the most clinically mature nano-delivery systems, featuring excellent biocompatibility, low immunogenicity and good biodegradability [7]. As representative amphiphilic vesicles, liposomes consist of phospholipid bilayers, capable of loading hydrophilic drugs in the aqueous core and hydrophobic drugs in lipid layers, enabling dual drug delivery and synergistic therapy [9]. Multiple FDA-approved liposome formulations have been widely used in clinical tumor treatment. Simple surface modification with pH/hypoxia/enzyme-sensitive groups endows liposomes with TME-responsive drug release ability [2]. However, their unstable bilayer structure can lead to premature leakage of the drug in the bloodstream, and storage accumulation limits subsequent clinical promotion. Polymer micelles with core-shell structures can effectively enhance the solubility of hydrophobic anti-tumor drugs and achieve drug release triggered by the TME, but the downside is their poor in vivo dilution stability. In contrast, solid lipid nanoparticles have high physical stability and low production cost. However, their lipid polymorphism properties can easily lead to sedimentation and leakage of drugs during storage, ultimately limiting large-scale clinical transformation [2].

3.2. Polymer-based nanocarriers

Polymer-based nanocarriers are highly customizable delivery platforms with flexible structural design, high drug loading capacity, and diverse TME-responsive properties, suitable for delivering chemotherapy drugs, photosensitizers, and gene therapeutics [9]. These nanocarriers enable on-

DOI: 10.54254/2753-8818/2027.MB37184

demand drug release against acidic, highly redox-active, and enzyme-rich TMEs by binding pH-sensitive groups and redox disulfide bonds or enzyme-cleavable peptides into polymer chains, avoiding premature drug leakage and reducing systemic toxicity [8]. The active targeting of tumors has been further enhanced through surface modification of the targeted ligand. Dendrimers, as branched polymer nanocarriers, feature uniform particle size and abundant modification sites, enabling extremely precise targeted drug delivery [10]. Recently, several polymer nano-formulations have entered clinical trials to test their potential use for cancer treatment. However, many synthetic polymer-based nano-systems are non-biodegradable and may exhibit toxicity, limiting their clinical applications. Furthermore, most synthetic polymers are difficult to prepare into nanosystems through simple methods, and the quality of the resulting products is unstable, which is very expensive for large-scale production. Therefore, at present, there are significant obstacles to the clinical transformation of most synthetic polymer-based nanosystems.

3.3. Inorganic nanocarriers

Inorganic nanocarriers, such as gold nanoparticles and mesoporous silica nanoparticles, are multifunctional systems for tumor diagnosis and therapy. Due to their unique optical and structural properties, inorganic nanocarriers are distinct from organic carriers. For instance, gold nanoparticles are biocompatible and have adjustable optical properties, and after surface modification, they can be used for a combination of photothermal tumor ablation and chemotherapy for synergistic therapy. In the meantime, the nanoparticles can be used for imaging of the tumor in real time [2, 8]. Mesoporous silica nanoparticles feature high specific surface area and controllable pore structures, achieving high-efficiency drug loading and TME-stimulated on-demand drug release with good biosafety [8]. However, poor in vivo biodegradability causes long-term accumulation of inorganic nanomaterials in metabolic organs, leading to potential chronic toxicity [10]. Additionally, complex synthesis procedures, high costs and unstable batch consistency confine most inorganic nanocarriers to preclinical research stages.

3.4. Biological nanocarriers

Exosome-based biological nanocarriers are natural endogenous nano-vesicles with unparalleled biosafety advantages over synthetic carriers, representing one of the most clinically promising delivery systems [10]. With a 30–150 nm lipid bilayer structure, exosomes exhibit ultra-low immunogenicity, excellent biocompatibility and inherent tumor homing ability, effectively avoiding in vivo immune clearance [2]. They can stably carry small-molecule drugs, proteins and nucleic acids, and penetrate multiple biological barriers to selectively accumulate in tumor tissues. Bioengineering modification further endows exosomes with TME-responsive release and immunosuppressive microenvironment remodeling functions [7]. Several exosome anti-tumor preparations have entered phase I clinical trials with verified safety. However, low purification yield, high preparation cost, unstable batch quality and unclear long-term metabolic safety severely restrict their large-scale clinical popularization [10].

3.5. Hybrid nanocarriers

Single-component nanocarriers inevitably have functional defects that limit comprehensive clinical application, while hybrid nanocarriers integrate the advantages of lipids, polymers, inorganic and biological materials to achieve complementary functions and multi-modal synergistic therapy [7].

DOI: 10.54254/2753-8818/2027.MB37184

Polymer-lipid hybrid carriers balance the structural stability of polymers and biocompatibility of lipids, solving the premature leakage defect of pure liposomes [2]. Cell membrane-coated hybrid nanocarriers can achieve immune escape and homologous tumor targeting abilities, which greatly improve how well tumors can accumulate these particles. These mixed systems can build multi-stimulus responsive structures to fit the complex features of the tumor microenvironment (TME), and achieve precisely controlled drug release plus combined diagnosis and treatment [10]. Even though these nanocarriers work really well, they still face big problems when it comes to translating them into real use: complicated multi-step preparation processes lead to bad repeatability between batches, make it hard to standardize quality, and push up the threshold for clinical approval. All of these get in the way of their industrial and clinical use.

4. Current challenges and optimization strategies of nanocarrier clinical transformation

4.1. Industrial production and batch stability problems

Large-scale standardized production is the main bottleneck that stops nanocarriers from being turned into clinical products. Most nanocarriers made in labs depend on careful manual work. When traditional methods are scaled up for bigger production, it causes big changes to particle size, how well particles disperse, and how much drug they can carry. This results in inconsistent quality between multiple batches and much higher costs, which do not meet the required standard of clinical drugs [11]. Currently, quality by design (QbD) frameworks and microfluidic technology can effectively optimize production stability. For QbD to achieve quantitative quality control, it standardizes key process parameters, meanwhile, microfluidic microchannel reactions ensure uniform nanoparticle synthesis and expected batch consistency. Additionally, artificial intelligence technology is now used to optimize formulation parameters, shorten R&D cycles, and enable real-time production monitoring, together effectively promoting industrial standardized production [9].

4.2. In vivo stability and drug release safety risks

In vivo circulation stability and controlled drug release safety are critical for clinical nanocarrier application. After intravenous administration, nanocarriers are exposed to a complex blood environment, including dilution, protein adsorption, and immune phagocytosis [11]. Conventional nanocarriers are prone to structural dissociation and premature drug leakage during circulation, causing systemic toxicity in normal tissues and insufficient tumor drug accumulation, thus reducing therapeutic efficacy and causing safety risks [11]. Multiple optimization strategies have been developed to address these issues. Multi-stimulus responsive structural design ensures carrier stability in normal tissues and precise on-demand drug release in TME. Hybrid structure optimization and PEGylation surface modification together form a protective hydration barrier, prevent immune clearance, prolong in vivo circulation time, and improve the efficiency of tumor enrichment. In addition, freeze-drying and standardized sterile purification technologies have effectively enhanced the storage stability and finished product safety of nanomedicines, supporting their safe clinical application.

4.3. Biosafety and in vivo metabolic risks

Biosafety and metabolic characteristics determine the clinical transformation value of nanocarriers. Ideal nano-drugs require excellent biocompatibility, complete in vivo degradation, as well as no

DOI: 10.54254/2753-8818/2027.MB37184

long-term toxic effects. However, most inorganic nanocarriers have poor degradability and accumulate long-term in the liver and spleen, which causes potential chronic inflammation and organ toxicity with unclear long-term metabolic mechanisms [10]. High-generation dendritic polymers also exhibit cytotoxicity from surface positive charges and in vivo accumulation risks of non-degradable skeletons [11]. Residual solvents and impurities in synthetic processes further compromise preparation safety. Current optimization strategies focus on adopting biodegradable materials such as PLGA, chitosan, and exosomes, which can be metabolized into non-toxic products in vivo to avoid accumulation toxicity. Optimizing particle size for renal clearance and establishing unified safety evaluation standards also effectively improve the clinical applicability of nanocarriers [12].

4.4. Insufficient in vivo therapeutic efficacy and transformation gap

A prominent preclinical-clinical transformation gap universally exists in TME-responsive nanocarrier research. Most nanocarriers exhibit excellent tumor targeting and anti-tumor efficacy in homogeneous animal models, but their therapeutic effects decline sharply in clinical trials, leading to frequent transformation failure [12]. The core reason is the huge discrepancy between preclinical animal models and heterogeneous human tumor microenvironments. Human tumors possess strong inter- and intra-tumor heterogeneity in pH, hypoxia and ECM density, while animal tumor models are highly unified and cannot simulate clinical complexity. Moreover, the human immune system has stronger foreign substance clearance ability, and human tumor vascular and stromal barriers are more stable, resulting in lower nanocarrier accumulation and penetration efficiency in vivo. Differences in cell endocytosis and drug metabolism between humans and animals further exacerbate efficacy inconsistency [12]. Developing bionic multi-stimulus responsive nanocarriers and patient-derived tumor models can effectively bridge this gap, promoting clinical translation.

5. Conclusion

TME-responsive intelligent nanocarriers break through the limitations of traditional tumor therapy by utilizing tumor-specific acidic, hypoxic and structural characteristics to achieve precise targeted drug delivery and microenvironment remodeling. Multiple nanocarrier systems have shown excellent application potential in overcoming tumor drug resistance and reducing systemic toxicity in preclinical studies. However, their clinical transformation is still restricted by unstable large-scale production, insufficient in vivo stability, unclear long-term biosafety and prominent preclinical-clinical gaps. Tumor heterogeneity and imperfect evaluation systems further limit industrialization and clinical popularization. Future research should focus on deepening the exploration of the biological mechanisms of TME, improving formulation accuracy by integrating artificial intelligence and multi-omics technologies, and optimizing the design of multi-response bionic nanocarriers. Meanwhile, strengthening interdisciplinary cooperation and establishing a standardized production and safety evaluation system will also effectively promote the clinical transformation of TME-responsive nanocarriers. Intelligent nanotherapy is in prospect to reshape the precise treatment paradigm of tumors and provide new strategies for efficient clinical tumor intervention.

References

[1] Sung, H., Filho, A. M., Laversanne, M., et al. Global cancer statistics 2024: GLOBOCAN estimates of incidence and mortality worldwide for 34 cancers in 186 countries. *CA Cancer J Clin.* 2026;e70090. doi:10.3322/caac.70090

DOI: 10.54254/2753-8818/2027.MB37184

[2] Aldhubiab, B., Almuqbil, R. M., & Nair, A. B. (2025). Harnessing the power of nanocarriers to exploit the tumor microenvironment for enhanced cancer therapy. *Pharmaceuticals, 18*(5), 746. https://doi.org/10.3390/ph18050746

[3] Piñeiro Fernández, J., Luddy, K. A., Harmon, C., & O'Farrelly, C. (2019). Hepatic tumor microenvironments and effects on NK cell phenotype and function. *International Journal of Molecular Sciences, 20*(17), 4131. https://doi.org/10.3390/ijms20174131

[4] Suzuki, K., Kachi, S., & Wada, H. (2026). Tumor microenvironment acidosis and alkalization-oriented interventions in advanced solid tumors: A narrative review and science-based medicine perspective on long-tail survival. *Cancers, 18*(8), 1193. https://doi.org/10.3390/cancers18081193

[5] Chen, Z., Han, F., Du, Y., Shi, H., Zhou, W. Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions. *Signal Transduct Target Ther.* (2023) 8:70. doi:10.1038/s41392-023-01332-8

[6] Mahaki, H., Nobari, S., Tanzadehpanah, H., Babaeizad, A., Kazemzadeh, G., Mehrabzadeh, M., Valipour, A., Yazdinezhad, N., Manoochehri, H., Yang, P., & Sheykhhasan, M. (2025). Targeting VEGF signaling for tumor microenvironment remodeling and metastasis inhibition: Therapeutic strategies and insights. *Biomedicine & Pharmacotherapy, 186*, 118023. https://doi.org/10.1016/j.biopha.2025.118023

[7] Fallatah, M. M., Alradwan, I., Alfayez, N., Aodah, A. H., Alkhrayef, M., Majrashi, M., & Jamous, Y. F. (2025). Nanoparticles for cancer immunotherapy: Innovations and challenges. *Pharmaceuticals, 18*(8), 1086. https://doi.org/10.3390/ph18081086

[8] Sheng, J., Yuan, W., Zhang, M. et al. Overcoming tumor microenvironment barriers: Transformable and bioinspired nanomedicine strategies for deep tumor penetration. *J Nanobiotechnol, 24*, 189 (2026). https://doi.org/10.1186/s12951-026-04028-7

[9] Wang, X., Li, C., Wang, Y., Chen, H., Zhang, X., Luo, C., Zhou, W., Li, L., Teng, L., Yu, H., & Wang, J. (2022). Smart drug delivery systems for precise cancer therapy. *Acta Pharmaceutica Sinica B, 12*(11), 4098–4121. https://doi.org/10.1016/j.apsb.2022.08.013

[10] Han, S., Chi, Y., Yang, Z., Ma, J., & Wang, L. (2023). Tumor microenvironment regulation and cancer targeting therapy based on nanoparticles. *Journal of Functional Biomaterials, 14*(3), 136. https://doi.org/10.3390/jfb14030136

[11] Dasare, M. K. D. S. N. R. M. a. B. . V. M. S. P. R. (2026). Nanoparticle in pharmaceutical drug delivery: Types, preparation, characterization, application, safety, and future perspective. *Zenodo* (CERN European Organization for Nuclear Research). https://doi.org/10.5281/zenodo.20471982

[12] Sureka, N., Maheshwari, R., Agravat, A., Singhal, S., Zaman, S., Rishi, B., Siraj, F., Zaheer, S., & Misra, A. (2026). Hypoxic microenvironment in cancer: Role in metabolic reprogramming. *Front. Oncol., 16*:1771365. doi: 10.3389/fonc.2026.1771365