REVIEW PAPER

Engineering Tumour Microenvironment-Responsive Nanocarriers to Overcome Bioavailability Barriers in Anticancer Therapy: Mechanisms, Advances, and Clinical Perspectives

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Abstract

Limited drug bioavailability remains one of the principal challenges in anticancer therapy, significantly compromising therapeutic efficacy due to poor aqueous solubility, rapid systemic clearance, non-specific biodistribution, inadequate tumor penetration, multidrug resistance, and the complex physiological barriers associated with the tumor microenvironment (TME). Recent advances in nanotechnology have enabled the development of tumor microenvironment-responsive nanocarriers that exploit unique pathological features of tumors, including acidic pH, hypoxia, elevated glutathione levels, enzyme overexpression, and oxidative stress, to achieve site-specific and stimuli-triggered drug delivery. This review comprehensively discusses the engineering strategies, physicochemical design principles, and functional mechanisms of TME-responsive nanocarriers, including pH-responsive, redox-responsive, enzyme-responsive, hypoxia-responsive, and multi-stimuli-responsive systems, with particular emphasis on their role in overcoming bioavailability barriers and improving therapeutic outcomes. The review further highlights advances in material selection, surface engineering, ligand-mediated targeting, controlled drug release, intracellular trafficking, and pharmacokinetic optimization that collectively enhance tumor accumulation, cellular uptake, and treatment efficacy while minimizing systemic toxicity. Furthermore, current challenges associated with tumor heterogeneity, biological barriers, manufacturing scalability, reproducibility, regulatory approval, and long-term safety are critically discussed to provide a realistic perspective on clinical translation. Emerging trends, including artificial intelligence-assisted nanocarrier design, biomimetic delivery systems, multifunctional theranostic platforms, and personalized nanomedicine, are also explored as promising strategies for the next generation of precision oncology. Overall, TME-responsive nanocarriers represent a transformative approach to overcoming the bioavailability limitations of conventional chemotherapy and hold significant potential for improving the safety, efficacy, and clinical success of targeted cancer therapeutics through intelligent and precision-guided drug delivery.

Keywords: Tumor microenvironment; TME-responsive nanocarriers; Bioavailability; Stimuli-responsive drug delivery; Cancer nanomedicine; Targeted drug delivery; Precision oncology; Controlled drug release.

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a significant global health burden despite continuous advancements in therapeutic strategies. Conventional anticancer treatments, including chemotherapy, are often limited by poor aqueous solubility, rapid systemic clearance, and non-specific biodistribution, which collectively result in reduced bioavailability and suboptimal

therapeutic efficacy [1,2]. These limitations have prompted the exploration of advanced drug delivery systems capable of improving therapeutic outcomes.

Furthermore, the non-selective nature of conventional drug delivery systems contributes to multidrug resistance (MDR), a major challenge in cancer therapy, ultimately resulting in poor clinical outcomes. These challenges underscore the urgent need for advanced drug delivery systems that can selectively target tumor tissues, enhance drug bioavailability, and minimize off-target toxicity.

In this context, nanotechnology-based drug delivery systems have emerged as a promising approach to overcome these limitations. Among them, tumor microenvironment (TME)-responsive nanocarriers have gained considerable attention due to their ability to exploit unique tumor-specific physiological conditions for targeted and controlled drug release.

2. Background and Problem Statement

Most conventional anticancer drugs suffer from poor aqueous solubility, which significantly limits their bioavailability and therapeutic efficiency. Additionally, rapid systemic clearance and non-specific distribution often result in inadequate drug concentrations at the tumor site, thereby reducing treatment effectiveness. These pharmacokinetic and biodistribution challenges frequently necessitate higher drug doses, which in turn increase the risk of systemic toxicity and adverse side effects. Furthermore, such limitations contribute to the development of multidrug resistance (MDR), ultimately leading to poor clinical outcomes in cancer patients [2,3]. Therefore, there is a critical need for the development of advanced drug delivery systems that can enhance drug targeting, improve bioavailability, and minimize off-target toxicity.

3. Tumor Microenvironment (TME)

The tumor microenvironment (TME) is a highly complex and dynamic network composed of cancer cells, stromal cells, immune cells, extracellular matrix components, and various signaling molecules. It significantly differs from normal physiological conditions and plays a crucial role in tumor progression, metastasis, and therapeutic resistance [4].

One of the hallmark features of the TME is its acidic extracellular pH, typically ranging from 6.5 to 6.8, which arises due to enhanced glycolysis and lactic acid production in cancer cells [5]. In addition, hypoxic conditions are commonly observed due to inadequate and abnormal tumor vascularization, further contributing to tumor aggressiveness and resistance to conventional therapies [6].

Another important characteristic of the TME is the presence of elevated intracellular levels of glutathione (GSH), creating a highly reductive environment that can be exploited for redox-responsive drug delivery systems [7]. Moreover, the overexpression of proteolytic enzymes such as matrix metalloproteinases (MMPs) and cathepsins facilitates tumor invasion and metastasis while also serving as potential biological triggers for enzyme-responsive nanocarriers [8].

Figure 1 illustrates, the tumor microenvironment (TME) highlighting key physiological and biochemical characteristics, including acidic pH, hypoxia, elevated glutathione (GSH) levels, and overexpression of proteolytic enzymes (MMPs, cathepsins), which collectively act as endogenous triggers for stimuli-responsive nanocarrier-based drug delivery systems

These distinct biochemical and physiological characteristics of the TME provide valuable endogenous stimuli that can be strategically utilized for the design of stimuli-responsive nanocarrier systems, enabling site-specific drug release and enhanced therapeutic efficacy.

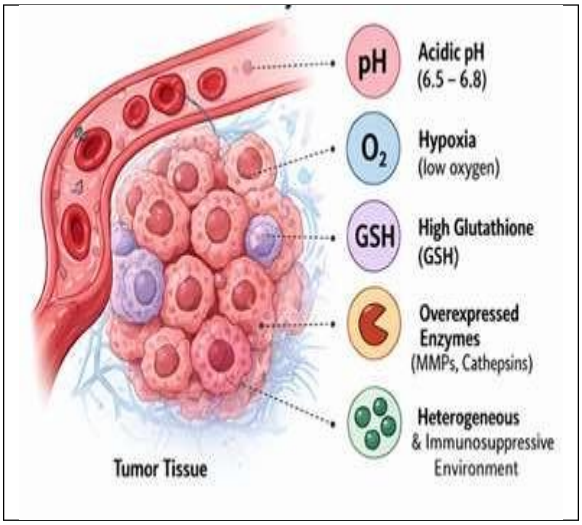

Figure:1: Schematic illustration of the tumor microenvironment (TME)

5. Types of Nanocarriers

Various nanocarrier platforms have been developed to improve drug delivery efficiency, stability, and targeting capability. Among them, liposomes are widely used due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs. Polymeric nanoparticles offer structural versatility and controlled drug release profiles, while

solid lipid nanoparticles (SLNs) enhance drug stability and reduce toxicity [12].

Additionally, dendrimers and hybrid nanocarriers provide precise surface functionalization and enable multi-drug delivery. These nanocarrier systems can be further engineered to respond specifically to tumor microenvironment stimuli, enhancing their therapeutic potential,figure 2 [13]. A comprehensive comparison of different nanocarrier systems along with their stimuli-responsiveness, mechanisms, and therapeutic advantages is summarized in Table 1.

6. Types of TME-Responsive Nanocarriers

6.1 pH-Responsive Nanocarriers

pH-responsive nanocarriers are designed to exploit the acidic nature of the tumor microenvironment. These systems incorporate acid-sensitive linkages such as hydrazone, imine, or acetal bonds that remain stable under physiological pH (~7.4) but undergo degradation in acidic conditions (pH 6.5–6.8) [14].

Upon reaching the tumor site, the acidic environment triggers drug release from the carrier, ensuring selective delivery to tumor tissues while minimizing exposure to healthy cells. This targeted release enhances therapeutic efficacy and reduces systemic toxicity [15].

6.2 Redox-Responsive Nanocarriers

Redox-responsive nanocarriers utilize the elevated intracellular glutathione (GSH) levels found in tumor cells. These carriers are typically designed with disulfide bonds that remain stable in the bloodstream but are cleaved in the reductive intracellular environment [16].

The cleavage of these bonds results in rapid intracellular drug release, enhancing drug accumulation within cancer cells and overcoming drug resistance mechanisms. Additionally, these systems prevent premature drug release during circulation [17].

6.3 Enzyme-Responsive Nanocarriers

Enzyme-responsive nanocarriers are activated by enzymes that are overexpressed in tumor tissues, such as matrix metalloproteinases (MMPs) and cathepsins. These systems incorporate enzyme-cleavable linkers that facilitate drug release specifically at the tumor site [18].

This selective activation improves targeting efficiency, reduces off-target toxicity, and enhances therapeutic precision, making enzyme-responsive systems highly effective for cancer treatment.

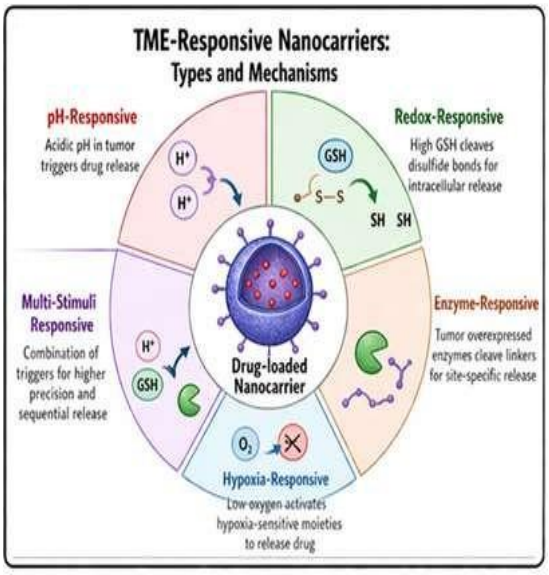

Figure:2: **Overview of different nanocarrier systems used in cancer therapy, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, and hybrid nanocarriers, highlighting their structural features and drug delivery capabilities**

6.4 Hypoxia-Responsive Nanocarriers

Hypoxia-responsive nanocarriers are designed to function under low oxygen conditions commonly observed in solid tumors. These systems incorporate hypoxia-sensitive moieties such as nitroimidazole, azobenzene, or quinone derivatives [19].

Under hypoxic conditions, these functional groups undergo chemical transformations that trigger drug release. This strategy is particularly effective for treating hypoxia-associated drug-resistant tumors and improving drug penetration into poorly vascularized regions [20].

6.5 Multi-Stimuli Responsive Nanocarriers

Multi-stimuli responsive nanocarriers integrate two or more triggers, such as pH, redox, and enzyme responsiveness, to achieve highly controlled and sequential drug release [21].

By responding to multiple tumor-specific conditions, these systems significantly enhance targeting precision, minimize premature drug release, and improve therapeutic outcomes. They are considered next-generation intelligent drug delivery platforms with high translational potential.

Table 1: Classification of nanocarriers and tumor microenvironment-responsive systems with mechanisms and therapeutic advantages

Nanocarrier Type	Stimulus Responsiveness	Mechanism	Key Advantages
Liposomes	pH, enzyme	Membrane destabilization in acidic TME	Biocompatibility, clinical use
Polymeric Nanoparticles	pH, redox	Polymer degradation, bond cleavage	Controlled release, tunability
Solid Lipid Nanoparticles (SLNs)	pH (limited)	Lipid matrix erosion	Stability, low toxicity
Dendrimers	pH, enzyme	Surface functional group cleavage	High drug loading, precision targeting
Hybrid Nanocarriers	Multi-stimuli	Combined mechanisms	Enhanced multifunctionality
pH-Responsive Systems	Acidic pH	Hydrazone/imine bond cleavage	Tumor-specific release
Redox-Responsive Systems	High GSH	Disulfide bond reduction	Intracellular drug release
Enzyme-Responsive Systems	MMPs, cathepsins	Enzyme-mediated linker cleavage	High specificity
Hypoxia-Responsive Systems	Low O_2	Nitroimidazole reduction	Deep tumor targeting
Multi-Stimuli Systems	Multiple triggers	Sequential/combined activation	High precision and efficacy

7. Bioavailability Barriers in Anticancer Therapy

The clinical success of anticancer therapy is largely dependent on achieving sufficient drug concentration at the tumor site while minimizing exposure to normal tissues. However, conventional anticancer agents frequently exhibit poor bioavailability due to multiple physicochemical, pharmacokinetic, and biological barriers. These limitations reduce therapeutic effectiveness and contribute to treatment failure, drug resistance, and systemic toxicity [22].

Bioavailability represents the fraction of administered drug that reaches systemic circulation and becomes available at the site of action. In cancer therapy, achieving optimal bioavailability is particularly challenging because tumors possess complex biological barriers, including abnormal vasculature, altered extracellular matrix composition, heterogeneous cellular populations, and immunosuppressive conditions are summarized in table 2 [23].

7.1 Poor Aqueous Solubility and Drug Instability

A significant proportion of anticancer drugs are hydrophobic molecules with limited aqueous solubility. Poor water solubility reduces dissolution rate, absorption efficiency, and distribution into tumor tissues. Drugs with low solubility often require the use of solubilizing agents or higher doses, which may increase toxicity and adverse reactions [24].

Furthermore, several anticancer molecules undergo chemical degradation or enzymatic metabolism before reaching the tumor site. Instability in biological fluids results in premature loss of therapeutic activity and reduces effective drug concentration.

7.2 Rapid Systemic Clearance and Metabolic Degradation

After administration, anticancer drugs are exposed to various clearance mechanisms including hepatic metabolism, renal filtration, and uptake by the mononuclear phagocyte system. Rapid clearance decreases plasma half-life and limits the duration of drug exposure to tumor cells [25].

Frequent dosing may compensate for rapid elimination; however, repeated administration often leads to accumulation of toxicity in healthy tissues. Therefore, strategies that enhance circulation time and protect drugs from premature degradation are essential.

7.3 Non-Specific Distribution and Off-Target Toxicity

Traditional chemotherapy relies mainly on passive drug distribution, resulting in drug exposure to both tumor and normal cells. Since many anticancer drugs interfere with essential cellular processes such as DNA replication and mitosis, non-specific distribution causes severe side effects including bone marrow suppression, gastrointestinal damage, and immune dysfunction [26].

An ideal drug delivery system should selectively transport therapeutic agents to tumor tissues while reducing exposure to healthy organs.

7.4 Tumor Vascular Barriers and Poor Drug Penetration

Although tumors exhibit abnormal blood vessels that allow nanoparticle accumulation through the enhanced permeability and retention (EPR) effect, drug penetration remains limited due to heterogeneous vascular distribution, dense extracellular matrix, and elevated interstitial pressure [27].

The dense stromal environment surrounding tumor cells acts as a physical barrier, preventing uniform drug diffusion and reducing therapeutic response.

7.5 Tumor Microenvironment-Mediated Resistance

The tumor microenvironment plays a crucial role in reducing anticancer drug efficacy. Hypoxia, acidic extracellular pH, altered redox status, and elevated enzyme activity contribute to cancer cell survival and resistance mechanisms [28].

Hypoxic regions promote expression of resistance-associated proteins, whereas acidic conditions can alter drug uptake and intracellular processing. These microenvironmental factors represent major challenges for conventional therapy.

7.6 Multidrug Resistance (MDR)

Multidrug resistance is one of the major causes of chemotherapy failure. Cancer cells develop resistance through increased expression of drug efflux transporters such as P-glycoprotein, enhanced DNA repair mechanisms, and inhibition of programmed cell death pathways [29].

Nanocarrier-based systems provide an opportunity to bypass MDR by improving intracellular drug accumulation and enabling controlled release directly within cancer cells.

Table 2. Major Bioavailability Barriers in Anticancer Therapy and Nanocarrier-Based Approaches

Bioavailability Barrier	Biological Consequence	Effect on Therapy	Nanocarrier Strategy
Poor aqueous solubility	Reduced dissolution	Low drug availability	Encapsulation within lipid/polymeric carriers
Chemical instability	Drug degradation	Reduced potency	Protective nanocarrier environment
Rapid clearance	Short half-life	Reduced tumor exposure	PEGylation and long circulating systems
Non-specific distribution	Healthy tissue exposure	Increased toxicity	Ligand-mediated targeting
Poor tumor penetration	Limited accumulation	Reduced efficacy	Size optimization and stimuli release
Hypoxia and acidic TME	Resistance development	Reduced response	TME-responsive activation
MDR mechanisms	Drug efflux	Treatment failure	Intracellular controlled release

Figure 3, illustrates major barriers including poor solubility, rapid systemic clearance, non-specific biodistribution, tumor penetration limitations, hypoxia, acidic environment, and multidrug resistance. TME-responsive nanocarriers overcome these limitations by improving circulation stability, tumor accumulation, targeted cellular uptake, and stimuli-triggered drug release.

8. Mechanisms by Which TME-Responsive Nanocarriers Improve Bioavailability

TME-responsive nanocarriers represent intelligent drug delivery platforms capable of recognizing tumor-specific abnormalities and releasing therapeutic agents selectively, table 3. These systems improve bioavailability by enhancing drug stability, increasing tumor accumulation, and providing controlled intracellular delivery [30].

8.1 Enhanced Drug Protection and Stability

Encapsulation of anticancer drugs within nanocarriers protects them from premature degradation, enzymatic metabolism, and chemical instability. The carrier system acts as a protective reservoir that maintains drug integrity during systemic circulation.

Lipid-based carriers, polymeric nanoparticles, and hybrid systems provide suitable environments for both hydrophilic and hydrophobic drugs, improving formulation stability and therapeutic availability.

8.2 Prolonged Circulation and Pharmacokinetic Improvement

Surface modification approaches such as PEGylation reduce recognition by immune cells and decrease rapid clearance. This increases circulation time and improves the probability of nanocarriers reaching tumor tissues [31].

Improved pharmacokinetic properties allow sustained drug exposure and reduce the requirement for frequent dosing.

8.3 Passive Tumor Targeting Through EPR Effect

Nanocarriers exploit tumor-associated vascular abnormalities through passive targeting. Increased vascular permeability and defective lymphatic drainage promote nanoparticle retention within tumor tissues.

However, the effectiveness of the EPR effect depends on tumor type, size, vascularization, and stromal composition.

8.4 Active Targeting Through Surface Engineering

Active targeting improves tumor specificity by attaching ligands that recognize overexpressed receptors on cancer cells.

Common targeting molecules includes, Folate receptors, Transferrin receptors, Peptides , Monoclonal antibodies ,Aptamers.

Ligand–receptor interactions enhance cellular uptake through receptor-mediated endocytosis, increasing intracellular drug concentration.

8.5 TME-Triggered Drug Release

The most important advantage of responsive nanocarriers is their ability to release drugs only under tumor-specific conditions.

I. pH-responsive release

Tumor tissues exhibit acidic extracellular pH due to increased glycolysis and lactic acid accumulation. Acid-sensitive bonds such as hydrazone and imine linkages enable selective drug release under these conditions [32].

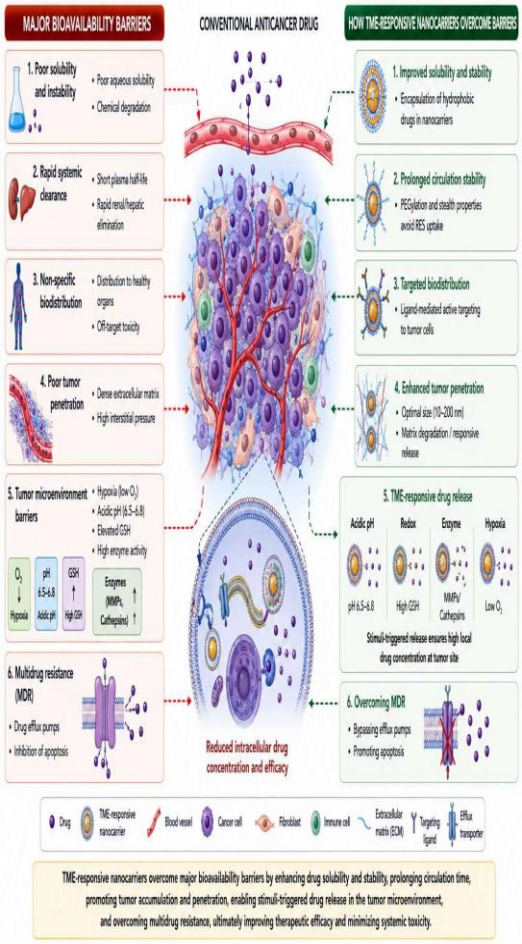

Figure 3. Bioavailability barriers in anticancer therapy and role of TME-responsive nanocarriers

II. Redox-responsive release

Cancer cells contain higher glutathione levels compared with normal cells. Disulfide-containing nanocarriers remain stable during circulation but undergo cleavage inside tumor cells, resulting in intracellular drug release.

III. Enzyme-responsive release

Tumor-associated enzymes such as matrix metalloproteinases and cathepsins can cleave specific linkers incorporated into nanocarriers, enabling selective activation [33].

IV. Hypoxia-responsive release

Hypoxic tumor regions activate oxygen-sensitive chemical groups, resulting in drug release specifically in low oxygen environments.

8.6 Overcoming Drug Resistance

Responsive nanocarriers increase intracellular drug accumulation and reduce drug efflux. Controlled release within cancer cells helps overcome resistance pathways and enhances apoptosis induction.

Table 3. TME-Responsive Nanocarriers and Their Contribution to Bioavailability Enhancement

Nanocarrier Type	Stimulus	Release Mechanism	Bioavailability Advantage
pH-responsive carrier	Acidic tumor pH	Bond cleavage	Tumor-specific release
Redox-responsive carrier	High GSH	Disulfide reduction	Intracellular delivery
Enzyme-responsive carrier	MMPs/cathepsins	Enzymatic cleavage	High specificity
Hypoxia-responsive carrier	Low oxygen	Chemical transformation	Deep tumor targeting
Multi-stimuli system	Multiple signals	Sequential activation	Improved precision

9. Challenges and Limitations

Although TME-responsive nanocarriers have shown promising results, several limitations must be addressed before widespread clinical application, table 4.

9.1 Tumor Heterogeneity

Tumors are highly diverse and vary in pH, oxygen level, enzyme expression, and vascular characteristics. This variability may reduce the efficiency of single-stimulus responsive systems [34]. Multi-stimuli responsive systems may provide better performance by recognizing multiple tumor-associated signals.

9.2 Manufacturing and Scale-Up Challenges

Large-scale preparation of nanocarriers with uniform size, stability, and reproducible drug loading remains difficult. Complex formulation procedures may affect commercial feasibility.

9.3 Safety and Toxicity Concerns

Long-term accumulation of nanoparticles, immune responses, and degradation products require extensive evaluation. Biocompatible and biodegradable materials are preferred to minimize toxicity.

9.4 Regulatory and Clinical Translation Barriers

Despite excellent preclinical outcomes, only limited nanocarrier systems successfully reach clinical use. Differences between animal models and human tumors remain a major challenge.

Table 4. Challenges and Future Solutions for Clinical Translation

Challenge	Impact	Future Solution
Tumor heterogeneity	Variable response	Personalized nanomedicine
Manufacturing complexity	Poor reproducibility	Scalable production methods
Safety concerns	Toxicity risk	Biodegradable materials
Limited clinical data	Slow approval	Advanced clinical studies
Resistance mechanisms	Reduced efficacy	Combination therapy

10. Future Perspectives

The future of TME-responsive nanocarriers lies in developing highly intelligent and personalized therapeutic systems.

Artificial intelligence and machine learning approaches can assist in predicting nanoparticle behavior, optimizing formulation parameters, and designing patient-specific delivery systems [35].

Integration of nanocarriers with immunotherapy, gene therapy, phototherapy, and combination chemotherapy may provide enhanced therapeutic outcomes.

Personalized nanomedicine approaches based on individual tumor profiles may allow selection of appropriate stimuli-responsive platforms for each patient.

Advanced multi-functional nanocarriers capable of simultaneous targeting, imaging, diagnosis, and therapy are expected to represent the next generation of precision oncology.

11. Conclusion

Tumor microenvironment-responsive nanocarriers provide a promising solution to overcome the major

bioavailability barriers associated with conventional anticancer therapy. Poor solubility, rapid clearance, non-specific distribution, tumor penetration limitations, and multidrug resistance significantly restrict treatment effectiveness.

By utilizing tumor-specific triggers including acidic pH, elevated glutathione concentration, enzyme overexpression, and hypoxia, responsive nanocarriers enable selective drug release and improved therapeutic concentration at tumor sites.

These advanced delivery systems enhance pharmacokinetic behavior, improve intracellular drug accumulation, minimize systemic toxicity, and support precision cancer therapy.

However, challenges related to tumor heterogeneity, manufacturing scalability, safety evaluation, and regulatory approval must be overcome. Future integration of artificial intelligence, personalized medicine, and advanced biomaterials is expected to accelerate the successful clinical translation of TME-responsive nanocarriers.

References: -

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020. *CA Cancer J Clin*. 2021;71(3):209–249.
2. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol*. 2007;2(12):751–760.
3. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress and perspectives. *Nat Rev Cancer*. 2017;17(1):20–37.
4. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression. *Nat Med*. 2013;19(11):1423–1437.
5. Webb BA, Chimenti M, Jacobson MP, Barber DL. Dysregulated pH in cancer. *Nat Rev Cancer*. 2011;11(9):671–677.
6. Vaupel P, Mayer A. Hypoxia in cancer. *Cancer Metastasis Rev*. 2007;26(2):225–239.
7. Estrela JM, Ortega A, Obrador E. Glutathione in cancer biology. *Crit Rev Clin Lab Sci*. 2006;43(2):143–181.
8. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases in cancer. *Cell*. 2010;141(1):52–67.
9. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. *Nat Mater*. 2013;12(11):991–1003.
10. Raza A, Hayat U, Rasheed T, Bilal M, Iqbal HMN. "Smart" materials-based near-infrared light-responsive drug delivery systems. *J Control Release*. 2019;297:82–103.
11. Torchilin VP. Multifunctional nanocarriers. *Nat Rev Drug Discov*. 2014;13(11):813–827.
12. Pattni BS, Chupin VV, Torchilin VP. New developments in liposomal drug delivery. *Chem Rev*. 2015;115(19):10938–10966.
13. Cheng CJ, Tietjen GT, Saucier-Sawyer JK, Saltzman WM. A holistic approach to targeting disease with polymeric nanoparticles. *Nat Rev Drug Discov*. 2015;14(4):239–247.
14. Bae YH, Park K. Targeted drug delivery to tumors. *J Control Release*. 2011;153(3):198–205.
15. Lee ES, Na K, Bae YH. pH-sensitive polymers for drug delivery. *J Control Release*. 2003;91(1–2):103–113.
16. Meng F, Hennink WE, Zhong Z. Reduction-sensitive polymers for intracellular drug delivery. *Biomaterials*. 2009;30(12):2180–2198.
17. Sun H, Guo B, Cheng R, Meng F, Liu H, Zhong Z. Reduction-responsive micelles. *Biomaterials*. 2009;30(31):6358–6366.
18. Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials. *Nanoscale*. 2014;6(21):12273–12286.
19. Thambi T, Park JH. Hypoxia-responsive nanocarriers. *Biomaterials*. 2014;35(5):1735–1743.
20. Brown JM, Wilson WR. Exploiting tumour hypoxia. *Nat Rev Cancer*. 2004;4(6):437–447.
21. Zhang P, Hu L, Yin Q, Feng L, Li Y. Smart nanodevices for cancer therapy. *Adv Mater*. 2016;28(33):7160–7173.
22. Allen TM, Cullis PR. Drug delivery systems: Entering the mainstream. *Science*. 2004;303:1818-1822.
23. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol*. 2007;2:751-760.
24. Torchilin VP. Multifunctional nanocarriers. *Nat Rev Drug Discov*. 2014;13:813-827.
25. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nat Biotechnol*. 2015;33:941-951.

26. Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics: An emerging treatment modality for cancer. *Nat Rev Drug Discov*. 2008;7:771-782.
27. Chauhan VP, Jain RK. Strategies for advancing cancer nanomedicine. *Nat Mater*. 2013;12:958-962.
28. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med*. 2013;19:1423-1437.
29. Gottesman MM. Mechanisms of cancer drug resistance. *Annu Rev Med*. 2002;53:615-627.
30. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. *Nat Mater*. 2013;12:991-1003.
31. Knop K, Hoogenboom R, Fischer D, Schubert US. Poly(ethylene glycol) in drug delivery: Pros and cons as well as potential alternatives. *Angew Chem Int Ed*. 2010;49:6288-6308.
32. Bae YH, Park K. Targeted drug delivery to tumors: Myths, reality and possibility. *J Control Release*. 2011;153:198-205.
33. Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials for controlled drug delivery. *Nanoscale*. 2014;6:12273-12286.
34. Vaupel P, Mayer A. Hypoxia in cancer: Significance and impact on clinical outcome. *Cancer Metastasis Rev*. 2007;26:225-239.
35. Li Y, Zhang X, Li H, Zhao Y. Artificial intelligence in nanomedicine: Opportunities and challenges. *Adv Drug Deliv Rev*. 2021;174:1-15.