Proceedings of ICBioMed 2026 Symposium: Advanced Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2025.AU38097

Mechanism and Progress of Stimulus-Responsive Nanoparticles in Targeted Cancer Therapy

Maonan Lu

School of Life Sciences, Ludong University, Yantai, China
1426845315@qq.com

Abstract. Cancer, a disease characterized by uncontrolled cell proliferation, poses significant challenges to traditional treatments. Surgery, chemotherapy, radiotherapy, and immunotherapy, while commonly used, are limited by issues such as difficulty in eliminating micro-metastasis, poor specificity with severe side effects, radiation damage to healthy tissues, and low patient response rates. Stimulus-responsive nanoparticles have emerged as a promising precision drug delivery strategy to address these limitations. They achieve targeted drug accumulation and controlled release by leveraging unique features of the tumor microenvironment (e.g., acidic pH, overexpressed enzymes like MMPs, and elevated ROS levels) and exogenous stimuli (e.g., light). Key types include pH-responsive nanoparticles, which rely on pH differences between tumor and normal tissues; enzyme-responsive nanoparticles, activated by specific overexpressed enzymes in tumors; and ROS-responsive nanoparticles, triggered by high ROS concentrations in the tumor microenvironment, each with distinct mechanisms and applications. However, their clinical translation faces challenges such as tumor microenvironment heterogeneity, biocompatibility concerns, insufficient drug release control, and limited tumor penetration. Future prospects lie in multi-stimulus synergistic therapy, intelligent and personalized design, combination with other therapeutic approaches, and the development of novel materials. This article reviews the mechanism, progress, challenges, and future directions of stimulus-responsive nanoparticles in targeted cancer therapy.

Keywords: stimulus-responsive nanoparticles, targeted cancer therapy, tumor microenvironment

1. Introduction

1.1. Cancer

1.1.1. What is cancer

Cancer is a type of disease caused by abnormal cell proliferation. Under normal circumstances, human cells grow, divide and die to maintain the normal function of tissues and organs. However, when mutations occur in the genetic material of cells, this can lead to uncontrolled cell proliferation and the formation of abnormal cell masses termed tumors. For example, under normal conditions,

© 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: 10.54254/2753-8818/2025.AU38097

lung cells follow predetermined procedures for growth, division, and apoptosis (natural death) to maintain the normal structure and function of lung tissue. However, if a gene in a lung cell – such as the p53 tumor suppressor gene that controls the cell cycle – mutates, the cell may lose its growth control. The mutated cell no longer follows normal division patterns but instead continues rapid proliferation without undergoing the normal death process (Fig. 1) [1].

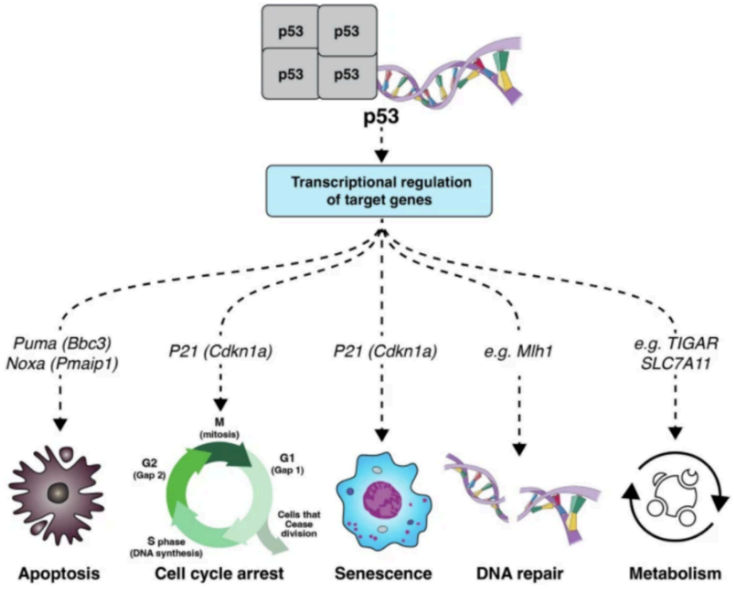


Figure 1. Cellular processes regulated by p53

1.1.2. Current status of cancer treatment

The severity of cancer lies not only in its direct damage to the body, but also in its aggressiveness, metastasis potential, and complexity of treatment. Despite advances in modern medicine in early cancer screening (e.g., colonoscopy screening for colorectal cancer) and precision treatments (e.g., immunotherapy, targeted drugs), the prognosis for advanced cancer remains suboptimal [2].

1.1.3. Recent advances in the treatment of tumors

The main treatments for cancer include surgery, chemotherapy, radiotherapy, and immunotherapy. Surgery involves direct surgical removal of visible tumor lesions, particularly effective for early-stage solid tumors (Fig. 2a). However, it struggles to eliminate microscopic metastases and shows limited efficacy in advanced diffuse tumors [3]. Chemotherapy uses cytotoxic drugs to inhibit cancer cell proliferation (Fig. 2b), but the lack of drug specificity leads to damage to normal proliferating tissues while eliminating cancer cells, causing severe toxic side effects that restrict treatment cycles and dosage [4]. Radiotherapy employs high-energy radiation to disrupt cancer cells' DNA structure(Fig. 2c), yet risks radiation damage to surrounding healthy tissues and demonstrates poor efficacy against drug-resistant tumors [5]. Immunotherapy utilizes drugs like PD-1/PD-L1 inhibitors to neutralize tumor-induced immune suppression, enabling immune cells to recognize and destroy cancer cells (Fig. 2d) [6]. However, patient response rates remain low at 20%-30%, with potential risks of immunological adverse reactions. While these traditional methods, including chemotherapy, have limitations such as limited efficacy or toxic side effects [2].Therefore, we need a better way to achieve accurate drug delivery. As a new precision drug delivery strategy, stimulus-responsive

DOI: 10.54254/2753-8818/2025.AU38097

nanoparticles can improve the efficiency of drug enrichment at tumor sites, reduce toxic and side effects on normal tissues through passive targeting, active targeting and stimulus-responsive release mechanisms, overcome drug resistance through multi-drug co-loading, and adapt to the tumor microenvironment to achieve personalized treatment, which provides an important path for breaking through the bottleneck of traditional treatment and promoting the development of precision medicine [7].

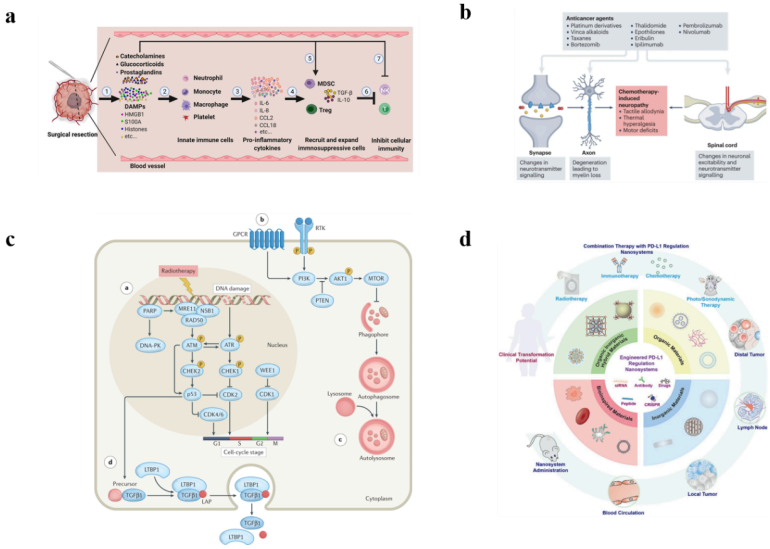


Figure 2. Mechanisms of current cancer treatments. (a) Surgery facilitates the formation of a tumor-supportive immune microenvironment. (b) Mechanism of non-specific toxicity of chemotherapy. (c)Mechanism of action of radiotherapy. (d) Design methods and mechanisms of nanoparticle anti-PD-L1 therapy

1.2. Stimulus-responsive nanoparticles

1.2.1. The rise of nanomedicine

Nanomedicine emerged in the 1990s with the cross-integration of nanotechnology and medicine. Advances in nanomaterial preparation technology led to nanoscale carriers that broke through the limitations of traditional drug delivery, establishing nanomedicine as an emerging discipline for disease diagnosis and treatment. Nanoparticles have significant advantages as drug carriers: surface modification or embedding can improve the solubility of poorly soluble drugs (e.g., paclitaxel nanoemulsions); Modifications such as PEGylation are used to evade clearance by the mononuclear phagocyte system (MPS) and prolong the blood circulation half-life beyond 24 hours; Nanoparticles exploit the enhanced permeability and retention (EPR) effect characteristic of solid tumors to passively accumulate at the tumor site. This results in a local drug concentration 3-5 times higher than that achieved with free drugs (such as conventional doxorubicin), promoting nanoparticles as a core platform for anti-tumor drug delivery.

1.2.2. Development of stimulus-responsive nanoparticle targeted therapy

With the rise of nanotechnology, nanoparticles as drug carriers bring new hope to solve these problems. Initially, although ordinary nanoparticles can achieve passive targeting to a certain extent, they still cannot meet the needs of efficient treatment. Subsequently, inspired by the complex

DOI: 10.54254/2753-8818/2025.AU38097

regulatory mechanisms in living organisms, researchers began to develop nanoparticles that can respond to specific stimuli. This evolution began with the early design of pH-responsive nanoparticles exploiting the pH gradient in the tumor microenvironment, and later expanded to include nanoparticles responsive to endogenous factors (such as redox potential and overexpressed enzymes) as well as exogenous stimuli (such as light, heat, and magnetic fields). The gradual development of these stimulus-responsive nanoparticles can enrich and release drugs at the tumor site more accurately, greatly improving the efficacy and safety of targeted cancer therapy, and becoming a promising research direction in the field of cancer treatment.

1.2.3. Working principle of stimulus-responsive nanoparticles

The endogenous response mechanism includes the use of the acidic pH of the tumor microenvironment, overexpressed enzymes (such as MMPs) and high concentrations of glutathione (GSH) to trigger the dissociation or degradation of the carrier structure, and the exogenous response uses external stimuli such as near-infrared light, magnetic field, ultrasound and other external stimuli to cause changes such as photothermal conversion, heat production or membrane rupture of the carrier Typical applications such as pH-sensitive doxorubicin liposomes and near-infrared light-responsive nanogels can significantly enhance anti-tumor efficacy.

1.3. Stimulus-responsive nanoparticles for cancer treatment

In modern cancer therapies, researchers have extensively developed and studied stimulus-responsive nanoparticles. These specialized nano systems can precisely target tumor microenvironmental factors such as low pH levels, overexpression of specific enzymes (e.g., matrix metalloproteinases, MMPs), elevated reactive oxygen species (ROS) concentrations, reduced glutathione levels, and light exposure, thereby enabling targeted drug delivery and controlled release.

2. Mechanisms of stimulus-responsive nanoparticles based on tumor microenvironment characteristics

2.1. Key features of tumor microenvironment

The tumor microenvironment (TME) is significantly different from the normal tissue microenvironment and possesses unique key features that serve as stimuli for the application of stimulus-responsive nanoparticles in targeted cancer therapy.

The tumor microenvironment exhibits acidic conditions pH. While normal tissues maintain an extracellular pH close to 7.4, tumor tissues typically exhibit pH values between 6.0 and 6.8. This acidity arises from the vigorous metabolism and rapid proliferation of cancer cells, which heavily rely on glycolytic pathways (Warburg effect) for energy production, generating substantial amounts of lactic acid [8]. Furthermore, abnormal vascular structures and impaired blood flow in tumors hinder the timely elimination of these acidic byproducts. Consequently, these metabolites accumulate extensively within the tumor microenvironment, leading to a significant decrease in pH levels.

The tumor microenvironment exhibits overexpression of specific enzymes. A prime example is matrix metalloproteinases (MMPs), whose expression and activity are significantly higher in tumor tissues compared to normal tissues [9]. Both tumor cells and surrounding stromal cells, immune cells, and others can secrete MMPs. During the growth, invasion, and metastasis of tumors, the

DOI: 10.54254/2753-8818/2025.AU38097

extracellular matrix (ECM) undergoes remodeling and degradation to facilitate cell migration and angiogenesis. In this process, MMPs play a pivotal role.

When reactive oxygen species (ROS) levels rise in the tumor microenvironment, cancer cells exhibit heightened metabolic activity, mitochondrial dysfunction, and frequent inflammatory responses. These conditions lead to significant accumulation of ROS such as superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (·OH). Nanoparticles containing ROS-sensitive chemical bonds like disulfide and thioether groups can penetrate this high-ROS environment. Upon entry, these sensitive bonds break down, causing structural disintegration of the nanoparticles and enabling effective drug release, thereby achieving therapeutic efficacy.

Furthermore, there exist numerous unique tumor microenvironments. For instance, light serves as an exogenous stimulus with excellent spatiotemporal controllability. Photodynamic therapy (PDT) operates on this principle: when exposed to specific wavelengths of light, photosensitizers are activated to produce reactive oxygen species (ROS), inducing immunogenic cell death in tumors and enhancing the body's anti-tumor immune response [10].The tumor microenvironment exhibits redox-responsive characteristics. Unlike normal cells, tumor cells maintain a relatively reduced intracellular environment due to higher levels of antioxidants like glutathione (GSH). Conversely, the extracellular tumor microenvironment shows relative oxidative states caused by accumulated ROS [11]. This redox gradient can be effectively harnessed.

2.2. PH-responsive nanoparticles

pH-responsive nanoparticles are a class of intelligent carriers that utilize the pH difference between tumor microenvironment and normal tissues to achieve targeted drug delivery. Their core mechanism is based on the significant difference in extracellular acidic microenvironments between tumor tissues and normal tissues.

For example, the pH/redox nanoparticle developed by Shi Jinfeng et al., composed of a hyaluronic acid-vitamin E succinate (HA-VE) shell and a disulfide-linked poly(β)-amino ester (PBAE) core. In the acidic tumor microenvironment (pH ~6.5) or within endosomes (pH ~5.5), protonation of the nanoparticle's amine groups occurs, leading to structural changes (Fig. 3a). This generates a "proton sponge effect" that facilitates nanoparticle escape from endosomes [12]. Wang Zhihao et al. investigated a nanoparticle system featuring an azo-bonded covalent organic framework (COF) core, surface-modified with a pH-sensitive sulfonamide-based zwitterionic polymer (PBA), and loaded with doxorubicin (DOX). In tumor microenvironment (pH 6.5), protonation of PBA causes surface charge to shift from-15.45 mV to + 12.24 mV (Fig. 3b). This electrostatic interaction enhances binding with tumor cells (negatively charged membrane) and promotes endocytosis [13].

These types of nanoparticles are typically engineered through chemical modifications to incorporate pH-sensitive groups (such as polyethylene glycol derivatives or poly-β-aminol esters) or acid-sensitive binding strategies. This design ensures structural stability at the physiological pH of the bloodstream, preventing premature drug leakage. When concentrated in tumor sites, the acidic environment triggers structural changes in the particles, including charge reversal, shell disassembly, or backbone degradation. These processes enable precise release of targeted therapeutic molecules like chemotherapy drugs, gene therapies, or photosensitizers, thereby enhancing drug concentration at tumor sites while reducing systemic toxicity.

DOI: 10.54254/2753-8818/2025.AU38097

2.3. Enzyme-responsive nanoparticles

Enzyme-responsive nanoparticles are smart carriers that enable precise drug release by leveraging the overexpression of specific enzymes in tumor microenvironments. Their mechanism operates through interactions between tumor-specific high-activity enzymes and enzyme-sensitive elements on nanoparticle surfaces or frameworks.

For example, Sun Yu's developed nanoparticles consist of a self-assembled paclitaxel (PTX) conjugate structure containing MMP-9-sensitive peptides (AGLDDRGD) and disulfide bonds. When exposed to tumor microenvironmentally elevated MMP-9 levels, these sensitive peptides undergo specific cleavage, causing the nanoparticles to transform from spherical (diameter ~48.9 nm) to rod-shaped (length ~297.1 nm). This morphological change enhances tumor cell uptake efficiency by 2.3 times compared to spherical nanoparticles, significantly improving the efficacy of drug-carrying molecules like paclitaxel in targeted tumor sites(Fig. 3c) [14]. Xiao Hong and colleagues developed a nanoparticle (PCL@GSK-diABZI/aPD-1) with surface-modified MMP-2-sensitive peptides linked to a PD-1 antibody (aPD-1). The matrix metalloproteinase-2 (MMP-2) in tumor tissues recognizes and cleaves these peptide-sensitive molecules, thereby releasing the nanomedicine (Fig. 3d) while retaining the PD-1 antibody on T cells for immune checkpoint blockade (ICB) therapy [15].

In healthy tissues, these nanoparticles maintain structural stability through low enzyme expression or activity, preventing premature drug release. Upon reaching tumor sites, tumor microenvironment enzymes (such as matrix metalloproteinases, elastases, and hyaluronidase) specifically recognize and cleave the nanoparticle surface's enzyme-sensitive substrates (e.g., peptides and polysaccharide chains), or degrade the particle's enzymatically sensitive framework. This triggers nanoparticle disassembly, structural collapse, or alterations in surface charge/hydrophobicity, thereby accelerating drug release from the payload. This mechanism enhances local drug concentration in tumors while minimizing toxic side effects on healthy tissues.

2.4. ROS responsive nanoparticles

ROS-responsive nanoparticles are smart carriers that utilize the abnormal elevation of reactive oxygen species (ROS) levels in tumor microenvironments for precision drug delivery, with their mechanisms closely tied to ROS accumulation in tumor tissues. Due to hypermetabolism, mitochondrial dysfunction, and inflammatory responses, tumor cells exhibit significantly higher extracellular ROS concentrations (up to 2-10 times normal levels) compared to healthy tissues.

For instance, Kim Nuri et al. developed the t-pHUDs nanoparticle, which consists of a polymer core containing peroxalate ester bonds (pHU) and surface-modified taurine deoxycholic acid (TUDCA). The TUDCA binds specifically to tumor cells' high-expressing P-Selectin through its sulfate groups, enabling active targeting and enhancing nanoparticle accumulation in tumors (2.3 times higher than non-targeted nanoparticles). In tumor microenvironments rich in H_2O_2, the peroxanate bonds break down, releasing anti-angiogenic drug hydroxybenzyl alcohol (HBA), cell-protective ursodeoxycholic acid (UDCA), and the payload doxorubicin (DOX) (Fig. 3e). Here, DOX directly kills tumor cells, while HBA inhibits vascular endothelial growth factor (VEGF) to block tumor angiogenesis [16]. The R-MOF framework developed by Mao Yibin and colleagues is a hafnium-based nanoscale metal-organic framework constructed from two ligands: a quaternary amine (QP) ligand functionalized with ROS-sensitive 3,5-dimethoxybenzyl carbamate linkers, and a photosensitizer ligand, 5,15-diphenylphthalocyanine (DBP) . The QP ligand covalently binds to Toll-like receptor agonist R848 via these linkers. When exposed to 630 nm light, DBP generates

DOI: 10.54254/2753-8818/2025.AU38097

ROS (singlet oxygen and hydroxyl radicals). This dual mechanism enables direct tumor cell death through photodynamic therapy, while ROS-induced linkers cleavage enables controlled R848 release (Fig. 3f), ensuring precise therapeutic delivery at tumor sites [17].

These nanoparticles are typically constructed by incorporating ROS-sensitive chemical motifs (such as thioether bonds, borate ester bonds, or polythioethers) to form carrier structures that remain stable in the low-ROS environment of normal tissues. When targeted to tumor sites, high ROS concentrations oxidize these sensitive groups, causing chemical bond cleavage that leads to nanoparticle disintegration (e.g., from micelle disassembly into monomers or degradation of the nanoparticle framework). This triggers rapid drug release, enhancing local tumor drug concentration while reducing systemic toxicity.

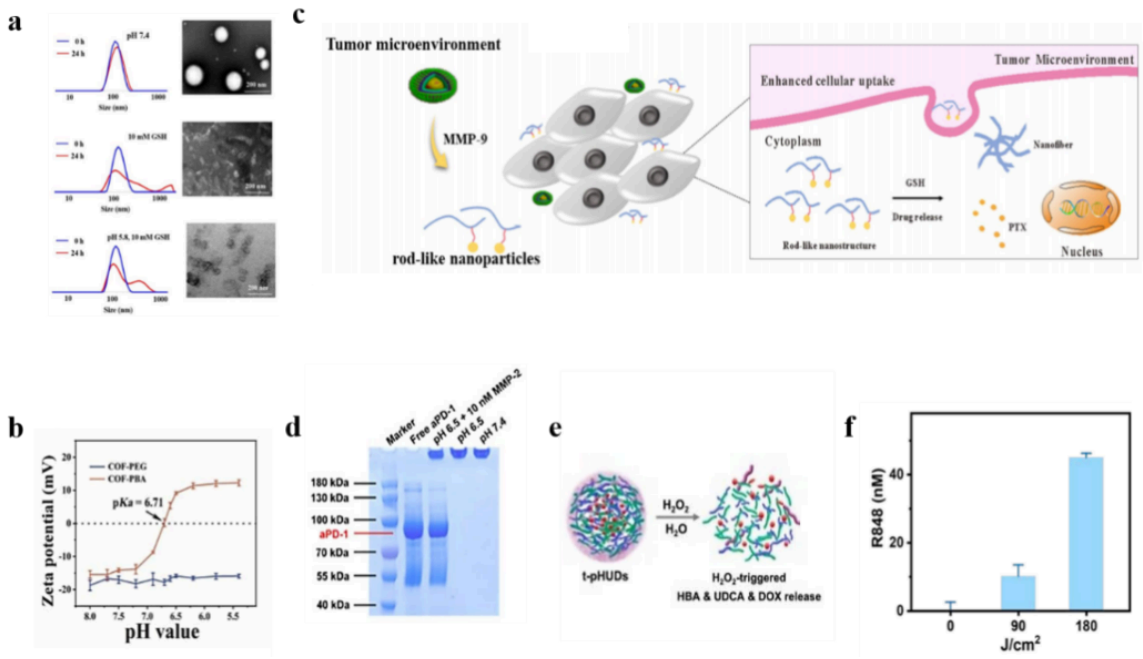


Figure 3. Mechanisms of stimulus-responsive nanoparticles. (a) Particle distribution by DLS and TEM image of TPL/NPs in response to different conditions. (b) Zeta potential of COF-PBA and COF-PEG in PBS at different pH. (c) Under the activation of MMP-9, the bond between AG and LDD cleaved, forming rod-like nanostructures. Due to their specific structure, cellular internalization of these nanostructures was enhanced, enabling intracellular PTX release. (d) Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDSPAGE) image of PCL-diABZI/aPD-1 pretreated with 10 nM MMP-2 for 4 h at an aPD-1 concentration of 20 μg. (e) In response to H2O2, t-pHUDs release DOX and decompose to liberate HBA and UDCA. (f) Power-dependent PDT-induced R848 release as analysed by LC-MS, confirmed that the ROS response triggered the release of R848

3. Discussion

3.1. Summary and comparison of stimulative response nanoparticles

Various types of stimulus-responsive nanoparticles exhibit distinct characteristics in cancer therapy, with core differences manifesting in stimuli, response mechanisms, and application scenarios. Commonly used stimulus-responsive nanoparticles (pH-responsive, enzyme-responsive, ROS-

DOI: 10.54254/2753-8818/2025.AU38097

responsive) all leverage inherent features of the tumor microenvironment to achieve targeted drug release, with each type exhibiting unique aspects in its mechanism, advantages, and limitations.

pH-responsive nanoparticles primarily utilize the pH difference between tumor tissues (pH 6.0-6.8) and normal tissues (pH 7.4). By protonating sensitive groups such as poly-β-amino esters and sulfonamide groups, they trigger charge reversal or structural disintegration to release drugs. Their advantage lies in requiring no external intervention and adapting to the common microenvironmental characteristics of most solid tumors. However, intra-tumor heterogeneity in pH levels (e.g., some regions maintaining near-normal pH) may reduce the response efficiency of pH-responsive nanoparticles and affect drug release stability.

Enzyme-responsive nanoparticles target the high expression of specific enzymes like matrix metalloproteinases (MMPs) in the tumor microenvironment. Through enzymatic cleavage of peptide segments and polysaccharide chains, they achieve disassembly and reassembly. This mechanism endows them with strong targeting specificity—for instance, nanoparticles containing MMP-9-sensitive peptides release drugs exclusively at tumor sites with high MMP-9 activity. However, inter-patient variability in enzyme expression levels (e.g., multiple-fold differences in MMP activity across different patients' tumor tissues) may lead to inconsistent therapeutic outcomes.

ROS-responsive nanoparticles leverage the tumor microenvironment's high concentration of reactive oxygen species (ROS)—typically 2-10 times higher than in normal tissues—to trigger drug release through oxidative cleavage of sensitive groups like thioether bonds and peroxalate ester bonds. These nanoparticles demonstrate rapid response capabilities and synergistic effects with ROS-related therapies such as photodynamic therapy (e.g., R-MOF nanoparticles releasing immunostimulants while generating ROS).

However, the elevated ROS levels observed in inflammatory areas of healthy tissues may lead to off-target drug release risks. While all these stimulus-responsive nanoparticles target tumor microenvironments, pH-responsive types emphasize broad applicability, enzyme-responsive types highlight specificity, and ROS-responsive variants combine both rapid response and synergistic potential. In practical applications, appropriate types can be selected based on dominant tumor microenvironment characteristics (such as significant acidity, specific enzyme overexpression, or ROS accumulation), or multi-mechanism combinations (e.g., pH/enzyme dual-response) can be employed to address more complex microenvironments, thereby enhancing the reliability of targeted drug release.

3.2. Challenges and limitations

At present, stimulus-responsive nanoparticles still face multiple challenges in clinical translation.

Tumor microenvironment heterogeneity: Significant variations exist in pH levels, enzyme activity, and ROS concentrations across different regions within a tumor. For instance, when certain tumor tissues exhibit pH levels similar to normal tissues, this may prevent pH-responsive nanoparticles from effectively triggering drug release. Moreover, significant differences in MMP expression levels among patients lead to unstable therapeutic efficacy of enzyme-responsive nanoparticles, reducing treatment consistency [18].

Biocompatibility and safety concerns: Some nanomaterials (e.g., metal-based nanoparticles) degrade slowly in vivo, potentially accumulating in organs like the liver and kidneys and causing toxicity. Additionally, surface-modified polymers or targeting molecules may trigger immune responses—such as the production of antibodies against PEG on coated nanoparticles—which accelerates clearance and reduces circulation time [19].

DOI: 10.54254/2753-8818/2025.AU38097

Insufficient drug release control: During systemic circulation, nanoparticles may experience premature drug leakage triggered by minor fluctuations in local conditions (e.g., pH), increasing systemic toxicity. Conversely, within the tumor tissue, insufficient stimulus intensity (e.g., ROS concentration below the activation threshold) can result in incomplete drug release and diminished efficacy [20].

Limited tumor penetration: The high interstitial fluid pressure and dense extracellular matrix (ECM) of solid tumors significantly hinder nanoparticle penetration. Even if accumulated around the tumor through the EPR effect, it is difficult to enter the deep tissues, resulting in insufficient drug concentration inside the tumor [21].

3.3. Future outlook

Although stimulus-responsive nanoparticles face many challenges in cancer treatment, their future prospects are still broad with the continuous development of materials science, nanotechnology and medicine.

Multi-stimulus-responsive synergistic therapy: Approaches relying on a single stimulus may be constrained by tumor microenvironment heterogeneity. In contrast, multi-stimulus-responsive nanoparticles can integrate both endogenous and exogenous stimuli to enhance the precision and efficiency of targeted drug release. For instance, designing nanoparticles that respond to both pH and near-infrared light allows them to maintain pH stability in the bloodstream. Upon reaching tumor sites, these particles rapidly release drugs under near-infrared irradiation while synergizing with photothermal therapy or photodynamic therapy to achieve comprehensive therapeutic effects [22].Furthermore, developing nanoparticles responsive to multiple stimuli can adapt to varying tumor microenvironment characteristics, thereby improving the universality of therapeutic applications.

Intelligent and Personalized Design: With the advancement of precision medicine, stimulus-responsive nanoparticles are evolving towards greater intelligence and personalization. By precisely analyzing patients' tumor microenvironment parameters—including tumor tissue pH, enzyme expression profiles, and ROS levels—nanoparticles can be customized for specific applications [23]. For instance, highly specific enzyme-responsive nanoparticles could be developed for tumors exhibiting elevated expression of particular MMPs. For tumors showing significant pH variations, the proportion of pH-sensitive groups in nanoparticles could be optimized. Additionally, leveraging the modifiable nature of nanoparticles, targeting molecules (such as antibodies or peptides) can be conjugated to their surface to enhance specific recognition of tumor cells, enabling personalized precision treatment [24].

Combination with other therapeutic approaches: Stimulus-responsive nanoparticles can synergize with surgery, radiotherapy, immunotherapy, and other modalities to enhance therapeutic outcomes. For example, when loaded with chemotherapeutic agents and immunological adjuvants, these nanoparticles release their payloads at tumor sites, directly killing cancer cells while activating the immune system to enhance treatment efficacy. When combined with radiotherapy, they act as radiosensitizers that enhance tumor sensitivity to radiation therapy. The drug release mechanism also helps minimize side effects associated with conventional radiotherapy.

Research and application of novel materials: Developing advanced nanomaterials with excellent biocompatibility, degradability, and functional properties represents a crucial future direction. For instance, natural polymers like chitosan and sodium alginate exhibit superior biocompatibility and biodegradability, making them ideal carriers for nanoparticles [25]. Stimulus-responsive smart polymers (such as shape-memory polymers) can adapt their structures to external stimuli, enhancing

DOI: 10.54254/2753-8818/2025.AU38097

the controllability of drug release [26]. Additionally, two-dimensional nanomaterials including graphene and black phosphorus possess large specific surface areas along with unique optical and electrical properties, demonstrating significant potential in designing stimulus-responsive nanoparticles [27].

In summary, stimulus-responsive nanoparticles represent a promising novel strategy for the precision treatment of cancer. With the continuous breakthrough of related technologies, it is expected to become an important means of cancer treatment in the future and bring new hope to cancer patients.

4. Conclusion

Stimulus-responsive nanoparticles, as an emerging targeted drug delivery system, offer significant potential for precision cancer treatment. By responding to specific signaling signals within and outside the tumor microenvironment, these systems can significantly enhance drug accumulation and release efficiency at lesion sites. This approach not only boosts anti-tumor efficacy but also reduces systemic toxic side effects.

While significant research progress has been achieved, clinical translation of nanomedicine still faces multiple challenges including tumor microenvironment heterogeneity, material biocompatibility, release control precision, and tissue permeability. Future research should focus on developing multi-stimulus-responsive synergistic strategies, advancing personalized and intelligent nano-drug design, enhancing combined applications with other therapeutic modalities, and promoting the development and application of novel biomedical materials.

In conclusion, stimulator-responsive nanoparticles are expected to become one of the key technologies in the field of cancer treatment. Through interdisciplinary collaboration and continuous innovation, this platform will accelerate clinical translation and provide more efficient and safe treatment options for cancer patients.

References

[1] Chen, T., Ashwood, L. M., Kondrashova, O., Strasser, A., Kelly, G., & Sutherland, K. D. (2024). Breathing new insights into the role of mutant p53 in lung cancer. *Oncogene, 44*(3), 115–129. DOI: 10.1038/s41388-024-03219-6.

[2] Brown, J. S., Amend, S. R., Austin, R. H., Gatenby, R. A., Hammarlund, E. U., & Pienta, K. J. (2023). Updating the definition of cancer. *Mol Cancer Res, 21*(11), 1142–1147. DOI: 10.1158/1541-7786.Mcr-23-0411 From NLM.

[3] Cheng, X., Zhang, H., Hamad, A., Huang, H., & Tsung, A. (2022). Surgery-mediated tumor-promoting effects on the immune microenvironment. *Seminars in Cancer Biology, 86*, 408–419. DOI: 10.1038/s41568-023-00610-5.

[4] Lustberg, M. B., Kuderer, N. M., Desai, A., Bergerot, C., & Lyman, G. H. (2023). Mitigating long-term and delayed adverse events associated with cancer treatment: Implications for survivorship. *Nature Reviews Clinical Oncology, 20*(8), 527–542. DOI: 10.1038/s41571-023-00776-9.

[5] Petroni, G., Cantley, L. C., Santambrogio, L., Formenti, S. C., & Galluzzi, L. (2021). Radiotherapy as a tool to elicit clinically actionable signalling pathways in cancer. *Nature Reviews Clinical Oncology, 19*(2), 114–131. DOI: 10.1038/s41571-021-00579-w.

[6] Kirthiga Devi, S. S., Singh, S., Joga, R., Patil, S. Y., Meghana Devi, V., Chetan Dushantrao, S., Dwivedi, F., Kumar, G., Kumar Jindal, D., Singh, C., et al. (2024). Enhancing cancer immunotherapy: Exploring strategies to target the PD-1/PD-L1 axis and analyzing the associated patent, regulatory, and clinical trial landscape. *European Journal of Pharmaceutics and Biopharmaceutics, 200*. DOI: 10.1016/j.ejpb.2024.114323.

[7] Xu, J., Wang, P., Bai, Z., Cheng, H., Wang, R., Qu, L., & Li, T. (2024). Sustainable moisture energy. *Nature Reviews Materials, 9*(10), 722–737. DOI: 10.1038/s41578-023-00643-0.

[8] Ma, F., & Yu, W. (2025). The roles of lactate and lactylation in diseases related to mitochondrial dysfunction. *International Journal of Molecular Sciences, 26*(15). DOI: 10.3390/ijms26157149.

[9] Zhang, P., Gao, Y., Tao, R., Zheng, J., Fu, Y., He, Y., Meng, Q., & Lee, M. H. (2025). Membrane-anchored tissue inhibitor of matrix metalloproteinase (TIMP)-1 promotes cell death in head and neck cancer by inducing DNA

DOI: 10.54254/2753-8818/2025.AU38097

damage, accumulating collagen II and disrupting cell survival mechanisms. *International Journal of Biological Macromolecules, 310*. DOI: 10.1016/j.ijbiomac.2025.143558.

[10] Shen, Z., Ma, Q., Zhou, X., Zhang, G., Hao, G., Sun, Y., & Cao, J. (2021). Strategies to improve photodynamic therapy efficacy by relieving the tumor hypoxia environment. *NPG Asia Materials, 13*(1). DOI: 10.1038/s41427-021-00303-1.

[11] Guzonjić, A., Crevar, M., Simić, I., Samardzić, N., Krstić, V. Ć., Stevuljević, J. K., & Jovanović, D. (2025). Alterations in GSH/GSSG and CyS/CySS redox status in small cell lung cancer patients undergoing chemotherapy. *Discover Oncology, 16*(1). DOI: 10.1007/s12672-025-03251-2.

[12] Shi, J. F., Ren, Y. L., Ma, J. Q., Luo, X., Li, J. X., Wu, Y. H., Gu, H., Fu, C. M., Cao, Z. X., & Zhang, J. M. (2021). Novel CD44-targeting and pH/redox-dual-stimuli-responsive core-shell nanoparticles loading triptolide combats breast cancer growth and lung metastasis. *Journal of Nanobiotechnology, 19*(1). DOI: 10.1186/s12951-021-00934-0.

[13] Wang, Z. H., Cheng, Q. L., Jiang, X. D., Chu, X. Y., Li, B. C., Zhang, L. T., Wu, W. L., Li, J. B., & Narain, R. (2024). pH/hypoxia dual-stimuli responsive COF nanocarriers with reversible charge conversions for the accurate tumor-targeting and enhanced anticancer drug delivery. *Colloids and Surfaces A-Physicochemical and Engineering Aspects, 703*. DOI: 10.1016/j.colsurfa.2024.135277.

[14] Sun, Y. (2023). A sequential stimulus-responsive nanoparticle platform for enhanced tumor growth inhibition and efficient drug delivery. *Journal of Pharmaceutical Innovation, 18*(2), 426-436. DOI: 10.1007/s12247-022-09653-x.

[15] Xiao, H., Li, X., Liang, S., Yang, S., Han, S., Huang, J., Shuai, X., & Ren, J. (2024). Dual-responsive nanomedicine activates programmed antitumor immunity through targeting lymphatic system. *ACS Nano, 18*(17), 11070-11083. DOI: 10.1021/acsnano.3c11464.

[16] Kim, N., Kwon, S., Kwon, G., Song, N., Jo, H., Kim, C., Park, S., & Lee, D. (2024). Tumor-targeted and stimulus-responsive polymeric prodrug nanoparticles to enhance the anticancer therapeutic efficacy of doxorubicin. *Journal of Controlled Release, 369*, 351-362. DOI: 10.1016/j.jconrel.2024.03.046.

[17] Mao, Y., Lin, W., Tillman, L., Jiang, X., Bian, W., Wang, C., Fromme, T., & Weichselbaum, R. R. (2025). Light-triggered toll-like receptor activation in a nanoscale metal–organic framework for synergistic PDT and cancer immunotherapy. *Chemical Science*. DOI: 10.1039/d5sc03446a.

[18] Yang, Y., Chen, Y., Pei, P., Fan, Y., Wang, S., Zhang, H., Zhao, D., Qian, B.-Z., & Zhang, F. (2023). Fluorescence-amplified nanocrystals in the second near-infrared window for in vivo real-time dynamic multiplexed imaging. *Nature Nanotechnology, 18*(10), 1195-1204. DOI: 10.1038/s41565-023-01422-2.

[19] Andrews, J. P. M., Joshi, S. S., Tzolos, E., Syed, M. B., Cuthbert, H., Crica, L. E., Lozano, N., Okwelogu, E., Raftis, J. B., Bruce, L., et al. (2024). First-in-human controlled inhalation of thin graphene oxide nanosheets to study acute cardiorespiratory responses. *Nature Nanotechnology, 19*(5), 705–714. DOI: 10.1038/s41565-023-01572-3.

[20] Varnavides, G., Yacoby, A., Felser, C., & Narang, P. (2023). Charge transport and hydrodynamics in materials. *Nature Reviews Materials, 8*(11), 726–741. DOI: 10.1038/s41578-023-00597-3.

[21] Wang, X., Zhang, H., Chen, X., Wu, C., Ding, K., Sun, G., Luo, Y., & Xiang, D. (2023). Overcoming tumor microenvironment obstacles: Current approaches for boosting nanodrug delivery. *Acta Biomaterialia, 166*, 42–68. DOI: 10.1016/j.actbio.2023.05.043.

[22] Jia, X. N., Liu, D. M., Yu, C., Niu, N., Li, D., Wang, J., & Wang, E. K. (2022). Tumor microenvironment stimuli-responsive single-NIR-laser activated synergistic phototherapy for hypoxic cancer by perylene functionalized dual-targeted upconversion nanoparticles. *Advanced Science, 9*(30). DOI: 10.1002/advs.202203292.

[23] Li, S.-L., Hou, H.-Y., Chu, X., Zhu, Y.-Y., Zhang, Y.-J., Duan, M.-D., Liu, J., & Liu, Y. (2024). Nanomaterials-involved tumor-associated macrophages' reprogramming for antitumor therapy. *ACS Nano, 18*(11), 7769–7795. DOI: 10.1021/acsnano.3c12387.

[24] Sun, M., Chen, P., Xiao, K., Zhu, X., Zhao, Z., Guo, C., He, X., Shi, T., Zhong, Q., Jia, Y., et al. (2023). Circulating cell-free DNAs as a biomarker and therapeutic target for acetaminophen-induced liver injury. *Advanced Science, 10*(16). DOI: 10.1002/advs.202206789.

[25] Niu, Y., Gao, Y., Xiao, Z., Mao, C., Wang, H., Geng, Y., Ye, Y., & Kou, X. (2023). Preparation and characterisation of linalool oil-in-water starch-based Pickering emulsions and the effects of the addition of cellulose nanocrystals on their stability. *International Journal of Biological Macromolecules, 247*. DOI: 10.1016/j.ijbiomac.2023.125732.

[26] Mandal, A., Taylor, M. A. D., Weight, B. M., Koessler, E. R., Li, X., & Huo, P. (2023). Theoretical advances in polariton chemistry and molecular cavity quantum electrodynamics. *Chemical Reviews, 123*(16), 9786–9879. DOI: 10.1021/acs.chemrev.2c00855.

[27] Li, Z., Liu, Z., Sun, H., & Gao, C. (2015). Superstructured assembly of nanocarbons: Fullerenes, nanotubes, and graphene. *Chemical Reviews, 115*(15), 7046–7117. DOI: 10.1021/acs.chemrev.5b00102.