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Tumor Microenvironment-Responsive Nanoparticles for Cancer Therapy: Design Strategies and Recent Advances

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Abstract: The tumor microenvironment (TME) plays a critical role in cancer progression and therapeutic resistance and is characterized by features such as hypoxia, acidic pH, aberrant enzyme expression, and redox imbalance. These characteristics provide endogenous stimuli for the development of stimulus-responsive nanomedicine. TME-responsive nanoparticles can recognize specific physicochemical signals within tumor tissues, enabling targeted drug delivery and controlled release, thereby enhancing therapeutic efficacy while reducing systemic toxicity. This review summarizes recent advances in the design and application of TME-responsive nanoparticles, focusing on hypoxia-, pH-, enzyme-, and redox-responsive nanoplatforms. Their roles in multimodal synergistic therapy and the induction of regulated cell death are also discussed. Finally, current challenges related to biosafety, in vivo stability, and clinical translation are highlighted to provide insights for the future development of TME-responsive nanomedicine.

1. Introduction

Despite substantial advances in cancer diagnosis and treatment, achieving effective and selective tumor therapy remains a major challenge in modern oncology. Conventional therapeutic strategies often rely on nonspecific cytotoxic effects, which can lead to limited efficacy and undesirable damage to normal tissues. In addition, therapeutic resistance further complicates treatment outcomes, highlighting the need for more precise therapeutic approaches.

Nanomedicine has emerged as a promising strategy to improve cancer therapy by enhancing drug delivery and enabling controlled drug release. In particular, nanoparticle-based systems can facilitate tumor accumulation; however, strategies relying on passive targeting mechanisms, such as the enhanced permeability and retention (EPR) effect, often suffer from limited delivery efficiency and insufficient tumor penetration. Increasing evidence suggests that the tumor microenvironment (TME) plays a crucial role in tumor progression and therapeutic response. The TME is characterized by features such as hypoxia, acidic pH, abnormal enzyme activity, and redox imbalance, which can serve as endogenous stimuli for site-specific drug release.

In this context, TME-responsive nanoparticles have emerged as a promising strategy for precision cancer therapy. This review summarizes recent advances in TME-responsive

nanomedicine, focusing on major responsive mechanisms and representative nanoplatforms, and discusses current challenges and future perspectives.

2. Tumor Microenvironment

The initiation and progression of tumors are not solely determined by tumor cells but are also regulated by the tumor microenvironment (TME), which comprises multiple cellular and noncellular components [1,2].

The TME exhibits several characteristic features, including hypoxia, acidic pH, abnormal enzyme expression, and elevated levels of glutathione (GSH) and reactive oxygen species (ROS) [3–5]. These features not only influence tumor development but also provide endogenous stimuli for the design of TME-responsive nanomedicines.

Nanoparticles engineered based on these characteristics can respond to specific stimuli such as pH, redox conditions, enzymes, or hypoxia, enabling controlled drug release and targeted delivery to tumor sites. Such strategies improve therapeutic efficacy while reducing damage to normal tissues. The major physicochemical characteristics of the TME and their corresponding nanotherapeutic strategies are summarized in Figure 1.

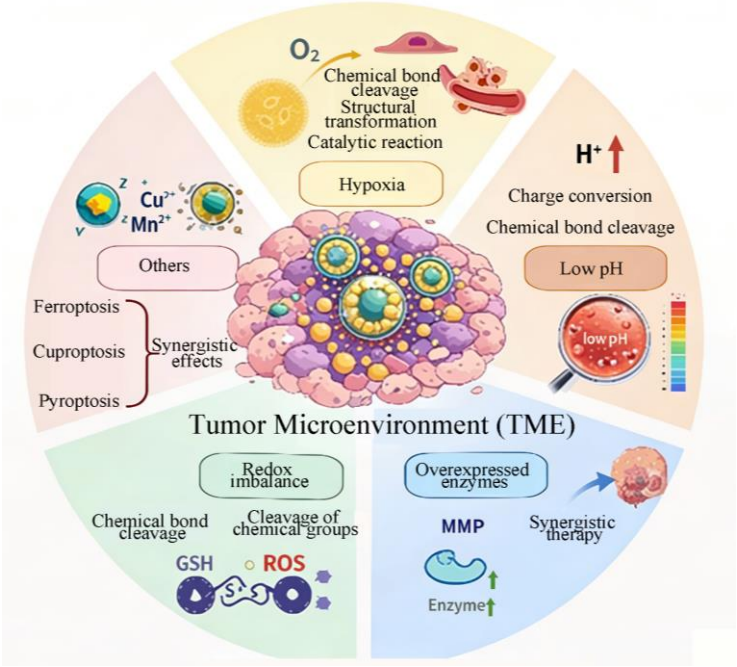

Figure 1: Tumor microenvironment characteristics and corresponding responsive nanoparticle strategies for cancer therapy

The tumor microenvironment is characterized by features such as hypoxia, acidic pH, redox imbalance (GSH/ROS), and abnormal enzyme expression. These stimuli can be exploited by responsive nanoplatforms to enable controlled drug release and enhance therapeutic efficacy, including the induction of regulated cell death.

2.1. Hypoxia

Hypoxia is a prominent feature of solid tumors, primarily resulting from rapid tumor growth and insufficient oxygen supply caused by abnormal angiogenesis and inadequate blood perfusion [6–8]. This hypoxic condition is closely associated with poor prognosis and reduced sensitivity to conventional therapies such as chemotherapy and radiotherapy [9,10].

At the molecular level, hypoxia stabilizes hypoxia-inducible factors (HIFs), particularly HIF-1α, which regulate tumor adaptation and progression [11,12]. Hypoxia also contributes to therapeutic resistance, as insufficient oxygen limits the generation of reactive oxygen species (ROS), thereby reducing the efficacy of treatments such as radiotherapy and photodynamic therapy [2,13].

2.2. Acidic Microenvironment

Tumor cells often exhibit metabolic reprogramming, characterized by enhanced glycolysis even under normoxic conditions, a phenomenon known as the Warburg effect. This process leads to the accumulation of lactate and acidification of the tumor microenvironment [14–16]. In addition, hypoxia and altered proton transport further contribute to the acidic conditions, resulting in a TME pH typically ranging from 6.5 to 6.9 [1,2].

An acidic microenvironment can promote tumor progression and reduce the efficacy of certain chemotherapeutic agents. More importantly, this characteristic provides a favorable basis for the development of pH-responsive drug delivery systems, enabling controlled drug release and improved therapeutic selectivity. Furthermore, the acidic microenvironment may contribute to immunosuppression within tumors [17].

2.3. Aberrant Enzyme Expression

Various enzymes are abnormally expressed in the tumor microenvironment and play important roles in tumor progression by regulating extracellular matrix remodeling, immune responses, and angiogenesis [8,18].

Among them, matrix metalloproteinases (MMPs) are widely recognized for their ability to degrade extracellular matrix components, thereby facilitating tumor cell migration and invasion and promoting tumor progression [19].

In addition, enzymes involved in immune regulation, such as indoleamine-2,3-dioxygenase (IDO) and cyclooxygenase-2 (COX-2), contribute to tumor immune evasion and angiogenesis [20,21]. Other enzymes are also implicated in tumor development and therapeutic resistance [10,22,23].

These abnormally expressed enzymes provide important biological triggers for the design of enzyme-responsive nanomedicine systems.

2.4. Redox Potential Differences (GSH and ROS)

Intracellular redox homeostasis is maintained by the balance between reactive oxygen species (ROS) and antioxidant systems, and its disruption can lead to oxidative stress and affect cell survival [12,24]. Tumor cells typically exhibit elevated levels of both ROS and glutathione (GSH) due to abnormal metabolic activity, contributing to therapeutic resistance [13,25].

ROS plays a dual role in tumor progression, as moderate levels promote cell survival, whereas excessive ROS can induce cell death [26,27]. The elevated levels of GSH and ROS in tumor tissues create a distinct redox gradient, which can serve as an important trigger for nanomedicine-based drug delivery systems [16].

Based on this characteristic, redox-responsive nanocarriers are designed to enable controlled drug release within tumor cells. Reduction-responsive systems commonly incorporate disulfide bonds (—S—S—), which are cleaved in high-GSH environments, while oxidation-responsive systems utilize ROS-sensitive linkers such as thioketal (TK) to trigger nanoparticle disassembly [17,28].

Overall, the redox characteristics of the tumor microenvironment provide an effective strategy for achieving targeted and controlled drug delivery.

3. Tumor Microenvironment-Responsive Nanoparticles

Tumor microenvironment (TME)-responsive nanoparticles are designed to achieve targeted drug delivery and controlled release by responding to specific stimuli within tumor tissues. Based on key characteristics of the TME, including hypoxia, acidic pH, abnormal enzyme expression, and redox imbalance, various responsive nanoplatforms have been developed, showing great potential in cancer therapy.

3.1. Hypoxia-Responsive Nanoparticles

Persistent hypoxia in the tumor microenvironment, once considered a major barrier to cancer therapy, is now recognized as an endogenous trigger for drug delivery. The low-oxygen and reductive conditions within tumors enable selective activation of hypoxia-responsive nanocarriers, allowing controlled drug release and improved therapeutic outcomes.

In a representative study, Thambi et al. developed a hypoxia-responsive polymeric nanoplatform based on 2-nitroimidazole-modified dextran for doxorubicin delivery. This system remained stable under normoxic conditions but rapidly disassembled in hypoxic environments, demonstrating effective tumor-targeted drug release in vivo [29]. Subsequently, various nanoplatforms have been designed using hypoxia-responsive moieties such as nitroaromatic groups, azo bonds, and N-oxide structures [25,27,30,31].

Recent advances have shifted from single-trigger systems toward multifunctional platforms that integrate diagnostic and therapeutic functions and address tumor heterogeneity [32,33]. For example, Yang et al. developed a BODIPY-based hypoxia-responsive nanosystem that combines chemotherapy with photodynamic and photothermal therapy. Under hypoxic conditions, azo bond cleavage triggers drug release, while light irradiation induces ROS generation and heat production, forming a synergistic therapeutic cascade [33].

Overall, hypoxia-responsive nanoparticles have evolved into multifunctional systems capable of both targeted drug delivery and tumor microenvironment modulation. However, challenges such as limited responsiveness and in vivo stability still hinder their clinical translation [34].

3.2. pH-Responsive Nanoparticles

The acidic characteristics of the tumor microenvironment provide an important basis for the design of pH-responsive nanoparticles. Due to the Warburg effect, tumor cells produce large amounts of lactate, resulting in a reduced pH (approximately 6.5–7.0) compared with normal tissues [35]. This pH difference enables selective drug release within tumor sites.

Early pH-responsive systems were mainly based on polymers containing ionizable functional groups that undergo protonation under acidic conditions, leading to structural changes and drug release. Typical materials include weakly acidic and basic polymers that can respond to pH variations and facilitate drug release or endosomal escape [36]. With continued development, these systems have evolved toward more precisely controlled and highly sensitive platforms capable of responding to subtle pH changes.

For example, Yao et al. developed an ultra-pH-sensitive nanoparticle system that undergoes rapid conformational changes when the pH decreases from 7.4 to 6.8, significantly enhancing drug release efficiency in tumor tissues [34]. In addition, pH-responsive polycarbonate nanoparticles (PEDHNPs) have been designed to enable sequential drug release through dual acid-sensitive linkages, thereby improving therapeutic efficacy [31]. Furthermore, other pH-responsive systems, such as functionalized mesoporous silica nanoparticles, have also demonstrated effective tumor-targeted drug delivery [37].

Overall, pH-responsive nanoplatforms have evolved from simple single-trigger systems to multifunctional platforms with improved responsiveness and therapeutic performance.

3.3. Enzyme-Responsive Nanoparticles

Enzyme-responsive nanoparticles represent an important class of intelligent drug delivery systems, as they can recognize and respond to enzymes overexpressed in the tumor microenvironment, thereby enabling targeted drug release and improved therapeutic specificity [11,35]. By incorporating enzyme-sensitive motifs into nanocarriers, it is possible to regulate drug release, structural transformation, and biological functions [38,39].

Among various enzyme targets, matrix metalloproteinases (MMPs) are the most widely studied due to their significant upregulation in many solid tumors. Nanocarriers incorporating MMP-cleavable peptide sequences can undergo site-specific degradation, facilitating drug release and enhancing tumor accumulation while minimizing damage to normal tissues.

With continued development, enzyme-responsive nanosystems have evolved from simple drug-release carriers into multifunctional platforms capable of improving tumor penetration, imaging, and immune activation. For example, enzyme-triggered structural changes, such as nanoparticle disassembly or aggregation, can enhance tissue penetration and retention within tumors [38].

In addition, enzyme-responsive systems have shown potential in cancer immunotherapy. For instance, a Cathepsin B-responsive nanosystem can induce lysosomal disruption and promote antigen presentation, thereby enhancing antitumor immune responses [40]. Furthermore, integrating enzyme responsiveness with other stimuli, such as pH or redox conditions, enables more precise spatiotemporal control of drug release.

Despite these advances, challenges such as limited in vivo stability, insufficient specificity, and difficulties in clinical translation remain. Overall, enzyme-responsive nanoparticles provide a promising strategy for precise drug delivery and multifunctional cancer therapy [41,42].

3.4. Redox-Responsive Nanoparticles

A prominent characteristic of tumor cells is the elevated intracellular levels of glutathione (GSH) and reactive oxygen species (ROS), which provide an important endogenous trigger for redox-responsive drug delivery. Compared with normal cells, tumor cells typically exhibit increased GSH and ROS levels, enabling selective activation of nanocarriers within tumor tissues.

Early studies focused on reduction-responsive systems based on disulfide bonds, which can be cleaved in high-GSH environments to trigger drug release. For example, Luo et al. developed a redox-responsive nanoplatform in which disulfide linkages enabled controlled intracellular release of doxorubicin, demonstrating the feasibility of redox-triggered drug delivery [43]. With further development, redox-responsive strategies have been extended to various nanocarriers, including polymeric and mesoporous systems, allowing improved control over drug release behavior.

Recent research has shifted toward multifunctional systems that combine redox responsiveness with other therapeutic modalities. For instance, integrating redox-triggered drug release with photodynamic or chemodynamic therapy can enhance therapeutic efficacy by simultaneously modulating the tumor microenvironment and increasing oxidative stress [44]. In addition, ROS-responsive systems capable of self-amplifying oxidative damage have been developed to further improve treatment outcomes.

Overall, redox-responsive nanoparticles can exploit the abnormal GSH/ROS balance in tumors to achieve controlled drug release and synergistic therapy. However, challenges such as limited specificity, stability, and clinical translatability remain to be addressed [45–47].

3.5. Responsive Nanoparticle Design for Synergizing Non-Apoptotic Cell Death

In recent years, several forms of non-apoptotic regulated cell death (RCD), including ferroptosis, cuproptosis, and pyroptosis, have attracted increasing attention due to their distinct mechanisms and strong immunogenicity. Tumor microenvironment (TME)-responsive nanoparticles can exploit tumor-specific signals to precisely induce and amplify these cell death pathways, thereby enhancing antitumor efficacy.

Ferroptosis, an iron-dependent form of cell death driven by lipid peroxidation, has been widely explored in nanomedicine. TME-responsive nanosystems can induce ferroptosis by increasing intracellular Fe^{2+} levels, depleting glutathione (GSH), or promoting reactive oxygen species (ROS) generation. For example, Fe^{2+}-based nanoplatforms combined with photothermal or chemodynamic therapy can enhance lipid peroxidation and improve therapeutic outcomes [48–51].

Other forms of RCD, such as cuproptosis and pyroptosis, have also been incorporated into nanoplatform design. Cuproptosis can be triggered by intracellular copper accumulation, while pyroptosis is associated with inflammatory responses induced by ROS or inflammasome activation. TME-responsive nanoparticles can regulate these processes through controlled release of metal ions or therapeutic agents, thereby improving tumor specificity and therapeutic efficacy.

More advanced strategies integrate multiple RCD pathways within a single nanoplatform to achieve synergistic effects. Overall, TME-responsive nanoparticles provide a promising approach for precise induction of non-apoptotic cell death and enhancement of antitumor immunity. However, further studies are needed to improve their safety, stability, and clinical translatability.

4. Conclusions

Tumor microenvironment (TME)-responsive nanoparticles have emerged as a promising strategy for precise cancer therapy, enabling targeted drug delivery and controlled release within tumor tissues. These systems have shown great potential in enhancing therapeutic efficacy and supporting multimodal treatment approaches. However, several challenges remain, including limited responsiveness and stability in complex tumor environments, insufficient tumor penetration, and difficulties in achieving precise spatiotemporal control. Future efforts should focus on improving nanocarrier design, integrating multiple responsive mechanisms, and combining these systems with immunotherapy and precision medicine strategies. With continued advances in nanotechnology and interdisciplinary collaboration, TME-responsive nanoplatforms are expected to accelerate the clinical translation of nanomedicine for cancer treatment.

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