

REVIEW PAPER

Research advances of tumor microenvironment-responsive nanomaterials for oral squamous cell carcinoma

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ABSTRACT

Introduction: Oral squamous cell carcinoma (OSCC) remains a main cause of morbidity and mortality in patients with head and neck squamous cell carcinoma (HNSC). Despite advances in clinical management, conventional therapeutic approaches are often accompanied by significant trauma and a high risk of recurrence.

Objective(s): The tumor microenvironment (TME) exhibits unique biochemical hallmarks. The rapid advancement of nanotechnology has facilitated the construction of TME-responsive nanoscale drug delivery systems (DDSs).

Materials and Methods: The TME is characterized by acidic pH, elevated glutathione (GSH) levels, dysregulated reactive oxygen species (ROS) metabolism, and overexpression of various tumor-associated enzymes (e.g., matrix metalloproteinases). These distinctive features collectively offer promising molecular targets for the development of targeted therapeutic strategies. The progress of nanotechnology also provides strong support for the construction of TME-responsive DDSs.

Results: While promising precision therapeutic strategies for OSCC continue to emerge, critical gaps remain. Herein, this paper presents a narrative review of TME-responsive DDSs for OSCC treatment, categorizing them by single- and multi-stimuli activation mechanisms and critically assessing the limitations of current nanomaterial-based approaches as well as their future directions.

Conclusion: In conclusion, additional efforts will be required in the future to accelerate the clinical translation of DDSs.

Keywords: Squamous cell carcinoma of head and neck; Tumor microenvironment; Nanostructures; Drug delivery systems

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INTRODUCTION

Oral cancer as one of the most prevalent cancers globally, the incidence sites include the tongue, buccal mucosa, floor of the mouth, gingival and other parts in the oral cavity. Notably, Oral squamous cell carcinoma (OSCC) accounts for more than 90%, and is the most common malignant tumor, with a high rate of recurrence and metastasis [1]. The 5-year survival rate is only 50 % to 60 %, which poses a serious threat to human health, and high recurrence rate and metastatic tendency are the key factors leading to poor prognosis of patients [2-5]. The occurrence and

progression of OSCC are strongly linked to various risk factors such as smoking [6], alcohol consumption [7], betel nut chewing [8], and human papillomavirus (HPV) infection [9]. At present, the clinical treatments are mainly surgery, radiotherapy and chemotherapy [10-13]. Nevertheless, these approaches often come with serious side effects and limitations [14]. Therefore, exploring novel therapeutic strategies that can significantly improve the quality of life and prognosis of OSCC patients has become an important direction in current research.

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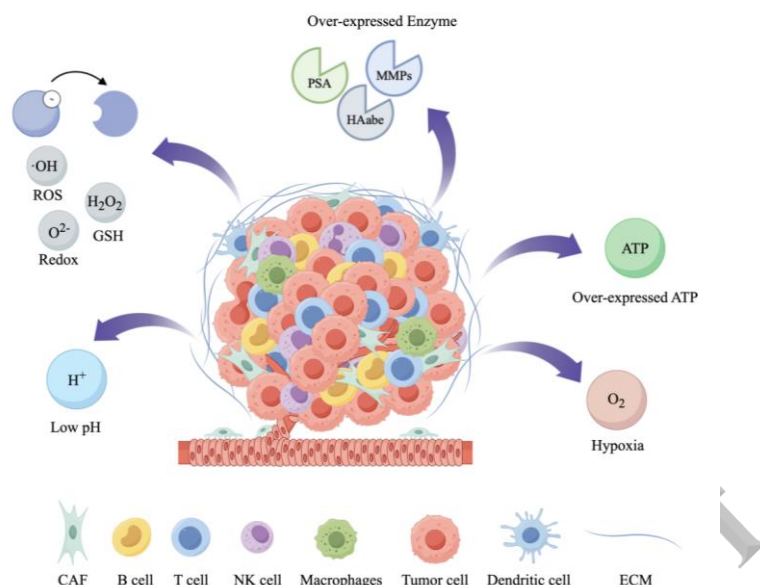


Fig. 1. Schematic diagram of characteristics of tumor microenvironment (by Figdraw).

As a central field of cancer research, the tumor microenvironment (TME) has received extensive attention in recent years. It plays an important role on tumor initiation, development, invasion, metastasis and drug resistance [15]. The TME consists of a variety of intertwined cellular and non-cellular components, with key components including immune cells, pericytes, tumor associated endothelial cells (TECs), tumor-associated fibroblasts (CAFs), extracellular matrix (ECM) and peripheral blood vessels (Figure 1) [16-18], which play a central regulatory role in the initiation and progression of OSCC [19,20]. Moreover, the TME exhibits a series of distinct characteristics, including acidic microenvironment (low pH), elevated glutathione (GSH) concentration, dysregulated reactive oxygen species (ROS) levels, local hypoxia, overexpression of certain specific enzymes, and high levels of adenosine triphosphate (ATP), etc. [21-24]. Based on the unique biological properties of the TME, drug delivery systems (DDSs) responsive to endogenous stimuli can be constructed for specific antitumor therapy [25].

The advancement of nanotechnology has offered ideal technical support for building such specific DDSs. According to the National Nanotechnology Initiative of the United States, nanotechnology is defined as the manipulation of materials with dimensions between 1 and 100 nm in at least one dimension [26]. In recent years, along with the progress in nanotechnology research and the increasing understanding of cancer biology and nano-biological interactions, a series of nanocarriers have been developed for cancer therapy [27]. Benefiting from their distinct size effect and surface modifiability, nanoparticles can

effectively respond to characteristic signals in the TME, including acidic pH, high concentration GSH, etc. [28]. By constructing TME-responsive nanocarriers, targeted enrichment and controllable release of drugs can be realized at the tumor site, thus significantly increasing the specificity of cancer therapy [29]. In contrast to traditional DDSs, nanocarriers demonstrate distinct superiorities in tissue penetration, drug loading efficiency, and tumor cell-targeting capability [30,31]. At present, they have been extensively applied to the precise delivery of therapeutic agents including chemotherapeutic drugs, nucleic acids, and genes [32].

Up to now, substantial progress has been made in designing intelligent DDSs for OSCC therapy. However, there is still no comprehensive review or summary work, particularly focused on TME-responsive tumor strategies based on various nanomaterials. Herein, in this review, the current research progress of GSH, pH, ROS, enzyme, and multi-responsive nanomaterials in the therapy of OSCC will be summarized, so as to offer a theoretical basis for the precise treatment of OSCC.

Categories of TME-responsive DDSs for OSCC therapy

GSH-responsive

GSH, as a critical endogenous antioxidant, plays an important role in various physiological and pathological processes [33,34]. The concentration of intracellular GSH is about 0.5-10 mM, while the amount of GSH in tumor cells is at least four to seven times higher than that in normal cells [35]. In the TME of OSCC, GSH levels are significantly elevated, which is mainly attributed to the

enhanced oxidative stress caused by the rapid proliferation and metabolic disorders of tumor cells [36]. In order to maintain intracellular redox homeostasis, tumor cells will abnormally increase the level of GSH by upregulating the GSH synthesis pathway [37,38]. Elevated GSH levels have dual effects: on the one hand, they can protect tumor cells from oxidative damage and guarantee survival and proliferation [39]. On the other hand, it will interfere with the effect of chemotherapy [40]. The majority of chemotherapy drugs take effect through intracellular redox reactions, but GSH can undergo chemical reactions with chemotherapy drugs, weakening their biological activity and ultimately inducing drug resistance in tumor cells, which brings obstacles to clinical cancer therapy [14,41].

Although elevated GSH levels in tumor cells impede the efficacy of cancer therapy, they simultaneously provide a unique opportunity for the development of GSH-responsive DDSs to enhance the therapeutic efficiency of cancer treatment. Studies have indicated that by incorporating GSH-responsive groups (such as disulfide bonds, diselenide bonds, etc.) [42-44], the reactive groups in DDS can specifically respond to high concentrations of GSH, resulting in the disassembly of nanomaterials or the release of loaded chemotherapy drugs [45,46]. Fan et al. [41] obtained GSH-sensitive and folic acid receptor (FA)-targeted DDSs by introducing disulfide bonds and folate molecules. After the DDSs enter the tumor cells through FA-mediated action, the disulfide bond in the DDSs is broken under the action of a high concentration of GSH, thereby releasing the loaded chemotherapy drug, which not only reduces the level of GSH but also increases the concentration of chemotherapy drug in tumor cells, significantly improving the therapeutic effect of OSCC.

Similarly, Jin et al. [47] constructed GSH-responsive nanomicelles using disulfide bonds as crosslinkers, with a shell composed of arginine/glucose oxidase (Arg/GOx) and a DOX core. Upon GSH exposure, the disulfide bonds are cleaved to release DOX, while GOx-catalyzed hydrogen peroxide production enhances nitric oxide (NO) generation. This system leverages the high GSH levels in the tumor microenvironment to achieve synergistic OSCC therapy while concurrently overcoming tumor drug resistance.

In summary, GSH-responsive nanomaterials effectively improve treatment efficiency by virtue of their accurate recognition and response ability to the TME, triggering drug targeted release, coordinating multiple treatment modes and other

mechanisms, thus providing a promising novel strategy for OSCC treatment.

pH-responsive

At present, pH-responsive nanomaterials have attracted researchers' attention in the field of OSCC treatment due to their unique properties and potential therapeutic value. Compared with normal tissues, abnormal pH values have become one of the most prominent characteristics of the TME in almost all types of tumors. This weak acid environment (pH 6.7 -7.1 [48]) is mainly attributed to the hypoxia in the tumor area and the excessive accumulation of lactic acid caused by rapid metabolism of cancer cells. Furthermore, the acidic condition can further enhance the proliferation, migration, and invasion capabilities of cancer cells [49-51]. This distinctive trait renders the weakly acidic pH as specific triggering stimulus for the design of locally environment-responsive nanomaterials [52].

In the treatment of OSCC, a variety of pH-responsive nanomaterials have shown promising application prospects. In addition to specifically responding to GSH, MnO₂ can also respond to low pH in the TME. In 2021, Zhou et al. [53] utilized MnO₂ as a nanocarrier for loading the chemotherapy drugs docetaxel and cisplatin (TP). MnO₂ can not only rapidly degrade and release TP in response to low pH, while significantly enhancing the T1-weighted images in Mn²⁺-mediated MRI, but also catalyze hydrogen peroxide (H₂O₂) to generate O₂, alleviating tumor hypoxia and improving the therapeutic efficacy of OSCC. In 2024, Zhao et al. [22] found that a pH-sensitive iron-based nanocomposite material can respond to the acidic microenvironment of the tumor and release therapeutic components during the treatment of OSCC. Moreover, the nanocomposite material is magnetic and can be used for MRI-guided therapeutic operations, further improving the precision of treatment. Li et al. [23] designed a pH-responsive nanoplatfrom using metal-organic framework (MOF) as the nanocarrier for the targeted therapy of OSCC. The carrier achieves therapeutic effects by pH-dependently releasing berberine and regulating the level of oxidative stress. Additionally, by utilizing the pH sensitivity of the MOF materials, the drug can achieve precise release in the acidic microenvironment of the tumor, while enhancing the killing effect on cancer cells by modulating oxidative stress. Cuprotoxis, as a novel cancer therapeutic approach, has shown tremendous application prospects in cancer treatment. In 2024, Ren et al. [54] constructed a nanosystem (ICG-ZIF-8-Cu) for the treatment of

OSCC by combining pH-responsive MOF material with cuprotoxicity. When ICG-ZIF-8-Cu is taken up by tumor cells, ZIF-8 undergoes lysis under the action of low pH, releasing copper ions (Cu^{2+}) and indocyanine Green (ICG), which are used to induce cuprotoxicity, immunogenic death, and photothermal therapy (PTT), respectively. This study utilizes a multimodal synergistic mechanism for the treatment of OSCC.

In addition to metal-based nanomaterials, graphene oxide-based nanomaterials have also attracted much attention in the field of pH-responsive nanomaterials. Multiple studies by Li et al. [55-57] have demonstrated that pH-responsive graphene oxide nanomaterials loaded with targeting peptides and anticancer drugs can achieve chemo-photothermal synergistic therapy for OSCC. Such nanomaterials can specifically recognize the weakly acidic pH and release drugs in the TME. Meanwhile, with the excellent photothermal conversion performance of graphene oxide, heat is generated under near-infrared light irradiation to further kill tumor cells, realizing synergistic therapeutic effect.

Stimulus-responsive polymers have attracted considerable attention as functional materials for DDSs. As pH-responsive cleavable groups, boronate ester bonds have been investigated in pH-responsive DDSs [58,59]. Yang et al. [60] designed macrophage membrane-encapsulated poly (methyl vinyl ether alt maleic anhydride)-phenylboronic acid-doxorubicin nanoparticles (MM@PMVEMA-PBA-DOX NPs, MM@DOX NPs) to dramatically improve the uptake efficiency of nanoparticles through macrophage membrane-mediated tumor targeting. The boronate ester bond between PBA and DOX can respond to the low pH in the TME, thereby enabling the selective release of loaded doxorubicin (DOX) for the specific treatment of OSCC. Neoadjuvant chemotherapy, as an adjuvant cancer treatment method, has been applied in the treatment of a variety of solid tumors. Several studies have shown that neoadjuvant

chemotherapy can effectively improve the prognosis of patients[61]. However, in the clinical treatment of OSCC, patients receiving cisplatin neoadjuvant therapy still face poor lymph node response and even lymph node progression. In order to explore the underlying mechanisms, Huang et al. [61] developed a pH-responsive nanoplateform capable of systemic delivery of GSDMD siRNAs for downregulating GSDMD expression to inhibit tumor metastasis. This pH-responsive siGSDMD delivery system can effectively suppress the growth and metastasis of OSCC tumors through efficient in vivo silencing of GSDMD expression. Table 1 lists the types, size, cumulative drug release, and cell lines of pH-responsive DDSs for OSCC drug delivery.

Overall, pH-responsive nanomaterials have provided a new strategy for the treatment of OSCC through precise drug delivery and multimodal synergistic therapeutic mechanisms. With the continuous advancement of nanotechnology and materials science, such intelligent DDSs are expected to play more important role in clinical translation, offering safer and more effective treatment options for patients.

ROS-responsive

ROS refer to a class of chemically reactive oxygen-containing molecules, including superoxide anion (O_2^-), H_2O_2 , and hydroxyl radical ($\cdot\text{OH}$), etc [62-64]. As one of the unique hallmarks of cancer, hypoxia significantly alters the ROS level in tumor tissues, resulting in a much higher ROS level in cancer cells (up to 100×10^{-6} M) than in normal tissues ($\approx 20 \times 10^{-9}$ M [65]). In the occurrence and development of tumors, ROS exert a dual role: an appropriate amount of ROS can act as signaling molecules to participate in normal cellular physiological activities; however, when excessively accumulated, they induce oxidative stress responses, causing oxidative damage to biomacromolecules such as DNA, proteins, and lipids, thereby promoting tumor initiation, progression, and metastasis [66,67].

Table 1. pH-responsive DDSs for OSCC drug delivery

DDS	Size	Cumulative Drug Release	Cell lines	Ref
USPBNPs@MCSNs (UPM)	104.6nm	70%	CAL-27 and HN6 cells	[22]
MIL-101@BER/PEG-FA	162.09nm	70.22%	CAL-27 and KB cells	[23]
H-MnO ₂ -PEG/TP	258.65nm	DOC: ~90% DDP: ~100%	CAL-27 and SCC7 cells	[53]
ZIF-8-Cu	169.9nm	36.41%	MOC1 and CAL-33 cells	[54]
DOX@GO-HAN-HN-1 (GHHD)	293.2nm	88.3%	CAL-27 and HOK cells	[55]
DOX@NGO-BBN-AF750	Diameter: 0.5-5 μm , thickness: 0.8-1.2 nm	19.8%	HSC-3 cells	[56]
NPF@DOX	-	67%	CAL-27 and HOK cells	[57]
MM@PMVEMA-PBA-DOX NPs	292.7 nm	21%	SCC15 and HN6 cells	[60]
MM@DOX NP)				
NPs (siGSDMD)	100 nm	~100%	CAL-27 and HSC-6 cells	[61]

This feature is particularly prominent in solid tumors such as OSCC, where abnormally elevated ROS levels are prevalent in the TME. This is mainly associated with abnormal tumor cell metabolism, inflammatory responses, and stimulation from therapeutic modalities such as radiotherapy and chemotherapy[68,69].

The abnormal elevation of ROS levels in the TME provides important theoretical support for the design of ROS-responsive nanomaterials. Such nanomaterials can leverage the locally high ROS levels in the tumor to trigger drug release, structural transformation, or activation of active components, thereby achieving targeted therapy[70,71]. Due to the dual role of ROS, the design of ROS-responsive nanomaterials requires precise regulation of their interaction with the TME. On one hand, leveraging the adaptive survival mechanism of tumor cells against ROS[72], the responsive drug release from the materials enhances the level of oxidative stress, thereby disrupting the adaptive balance of tumor cells. On the other hand, it is necessary to avoid oxidative damage to normal tissues, which is closely associated with the "double-edged sword" characteristic of ROS in cancer prevention and treatment [73,74]. From the perspective of therapeutic strategies, the combination of ROS-mediated targeting mechanisms and the characteristic TME has rendered ROS-responsive nanomaterials as an important tool for regulating tumor oxidative stress and improving therapeutic specificity, opening up a new avenue for addressing the off-target issue of traditional chemotherapy[75].

In response to the high levels of ROS in the TME, several ROS-responsive groups (such as thioketal (TK) bonds, thioacetal (TA) bonds, thioether groups, and boronate ester bonds) have been introduced to construct ROS-responsive DDSs for the treatment of OSCC [76-78]. These ROS-responsive groups can undergo cleavage under the action of high ROS levels, leading to the collapse of the nanostructure and the release of active drugs [79]. In 2018, Shi et al. [80] designed prodrug-type ROS-responsive nanoparticles modified with polyethylene glycol (PEG) and linked by TK bonds for the targeted therapy of OSCC. These nanoparticles can efficiently accumulate at the tumor site, under the stimulation of a high-ROS microenvironment, the TK bonds cleave, triggering structural disintegration and drug release, thereby achieving synergistic therapy of PDT and chemotherapy for cancer. Studies have shown that through targeted delivery to enhance intratumoral accumulation and ROS-responsive release to improve therapeutic specificity, it significantly inhibits tumor growth, providing an effective strategy for combined therapy. In 2025, Ma et al. [81] combined ROS-responsive groups with sonodynamic therapy (SDT) to construct BNT-TK-DOX nanosystems to synergize piezocatalysis and chemotherapy for the treatment of OSCC. BNT generates cytotoxic ROS under ultrasound (US) irradiation to kill tumors and simultaneously triggers the cleavage of TK bonds to release DOX, significantly enhancing antitumor efficacy and biocompatibility through dual mechanism of action.

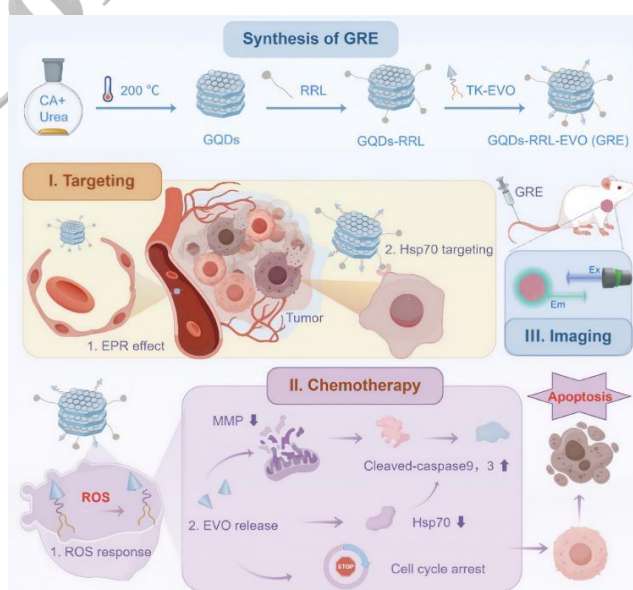


Fig. 2. Schematic illustration depicting the fabrication of biomimetic cascade-targeting GRE and its therapeutic mechanism of action [82]. Copyright 2025, Wiley-VCH GmbH.

Table 2. ROS-responsive DDSs for OSCC drug delivery

DDS	Size	Cumulative Drug Release	Cell lines	Ref
RPTD/HP	180nm	~70%	CAL-27 cells	[80]
BNT-TK-DOX	250 nm	-	HSC-3 cells	[81]
GQDs-RRL-EVO (GRE)	40-80 nm	40%	Cal-27 and SAS cells	[82]

In addition, nanosystems capable of exerting both therapeutic and localization functions have been one of the research focuses of investigators. Lv et al. [82] constructed biomimetic cascaded targeting nanoplateform (GQDs-RRL-EVO, GRE), which enhances GRE uptake through active and passive targeting strategies (Figure 2). Upon internalization into tumor cells, it responds to ROS to induce the cleavage of TK bonds, thereby releasing the drug. Furthermore, the intrinsic fluorescent properties of GQDs enable the precise release of the drug. This research, which integrates targeting, ROS-responsive release, and imaging functions into a single nanoplateform, provides an excellent paradigm for the treatment of OSCC. Table 2 lists the sorts, size, cumulative drug release and cell lines of ROS-responsive DDSs for OSCC drug delivery.

In summary, the high ROS characteristic in the TME of OSCC provides an ideal target for nanomaterials to achieve precise therapy. ROS-responsive nanomaterials have effectively improved tumor killing efficiency and therapeutic specificity by triggering controlled drug release, regulating redox balance, and synergizing combinatorial therapy. This lays a crucial foundation for the precise treatment of OSCC and the development of multifunctional combinatorial strategies.

Enzyme-responsive

Overexpression of enzymes such as matrix metalloproteinases (MMPs)[83], phospholipases [84] and glycosidases are also a major feature of TME, these enzymes accelerate tumor cell formation [85,86]. Among these, MMPs are the most representative, which are a family of zinc-dependent endopeptidases that remodel the ECM and participate in extracellular cell signaling [87,80]. Regulation of MMPs activity and expression at transcriptional and translational levels is essential and critical for maintaining normal biological processes [89]. Due to the functional diversity and ubiquity of MMPs, which can "shape" the TME through multiple pathways, creating favorable niche for tumor growth [90]. Consequently, they are regarded as prognostic biomarkers and therapeutic targets [91,92]. Since the 1990s, inhibiting MMPs has been a strategy for anticancer therapy, but with limited efficacy. In the past two decades, a novel therapeutic strategy targeting MMPs has been progressively developed. This approach capitalizes

on the intrinsic selective hydrolytic activity of proteases rather than inhibiting them, thereby enabling nanomaterials to exert potent anticancer efficacy.[93].

MMPs-responsive nanomaterials can achieve precise drug release at tumor sites by integrating MMPs-specific recognition sequences[86,94]. Hydrogel, as a material with three-dimensional network structure[95], can achieve drug encapsulation and in-situ formation at lesion sites, which can not only control the release of loaded drugs, but also greatly improve drug bioavailability and reduce drug toxicity. In 2019, Li et al. [96] developed an in situ formable hydrogel for delivering DOX. Owing to the incorporation of MMP-2 responsive peptides in the hydrogel, the high levels of MMPs in the TME can induce peptide cleavage, thereby enabling the precise release of DOX (Figure 3). In 2025, this research group [97] similarly developed MMP-2 responsive in-situ forming hydrogel for the co-encapsulation of two drugs, DOX and sunitinib for the treatment of postoperative recurrence of OSCC. In addition to MMP-2, MMP-9 has also been exploited as a target for designing MMP-9-responsive nanosystems for the treatment of OSCC. In 2025, Xu et al. [98] loaded cobalt-manganese oxide nanocrystals (CMO NPs) into MMP-9-responsive gelatin to construct size-transformable and TME-activated nanoplateform. This nanoplateform was developed to address the limitations of traditional MRI contrast agents in OSCC therapy, including insufficient tumor penetration, poor accumulation, and single-modal imaging capability. Overexpressed MMP-9 in OSCC can degrade the gelatin shell, thereby releasing CMO NPs to exert both imaging and therapeutic effects.

Although enzyme-responsive strategies such as cathepsin B and hyaluronidase have been explored in other tumor types, their application in OSCC remains extremely limited. Therefore, this review focuses on MMP-responsive drug delivery systems for OSCC treatment. MMP-responsive nanomaterials offer a promising strategy for precisely regulating drug release in OSCC therapy. With the advancing integration of nanotechnology and tumor immunology, MMP-responsive nanomaterials are expected to become a key modality for multimodal OSCC treatment.

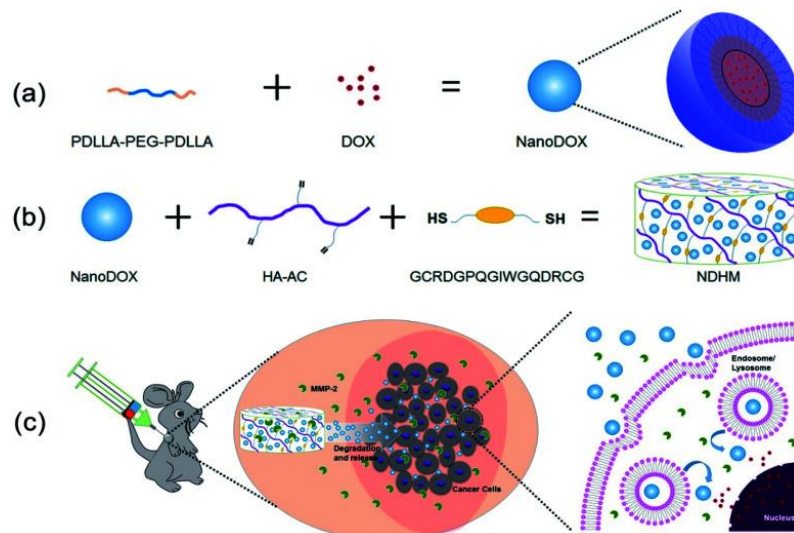


Fig. 3. (a-b) Schematic illustration of the synthesis process of MMP-responsive hydrogels encapsulating nano-DOX (NDHM). (c) Schematic Diagram of the Functional Mechanism of NDHM [96]. Copyright 2019, The Royal Society of Chemistry.

Multiple-responsive

With the continuous advancement of stimulus-responsive technology, researchers have established multi-stimuli-responsive systems by integrating different types of stimulus-responsive mechanisms [99]. These systems can integrate the advantages of various stimulus responses, more accurately perceive changes in the TME through multi-dimensional regulatory approaches, and more intelligently achieve precise regulation of the targeted drug delivery process. Meanwhile, they can flexibly regulate the drug release behavior at

the target site according to specific needs, thereby effectively overcoming the limitations of single-stimulus-responsive models and improving the precision and controllability of drug delivery and release.

Recently, the design of multiple stimulus-responsive nanomaterials based on the TME characteristics has become a hot research topic. For example, the GSH/pH dual-responsive copper-based cascade nanocomplexes (PLB-Cu@B-H) developed by Sun et al. [14] have been successfully applied to the treatment of OSCC (Figure 4).

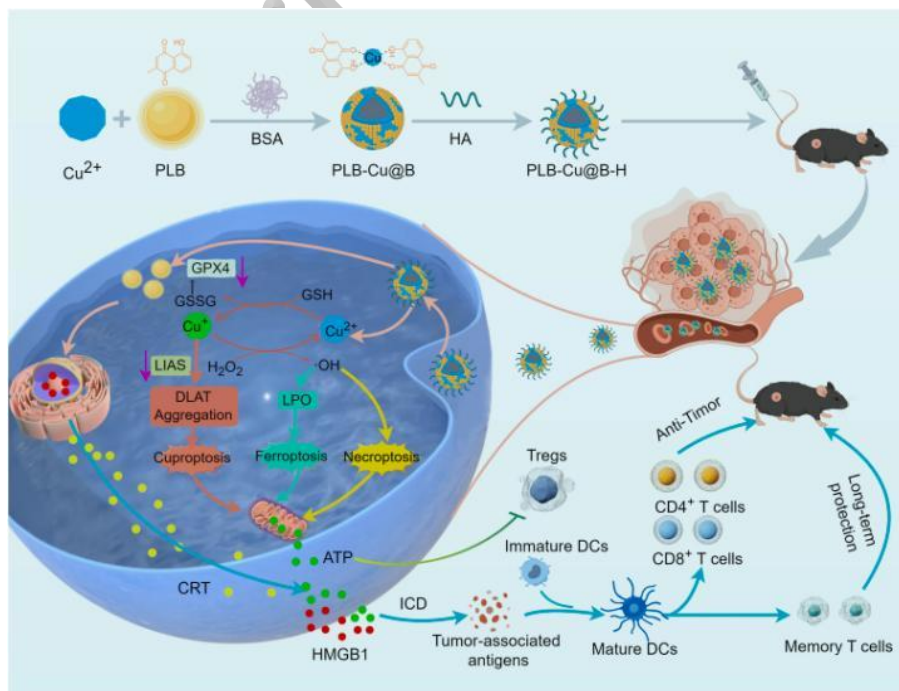


Fig. 4. Schematic illustration depicting the formation and therapeutic mechanism of GSH/pH-responsive copper-based cascade nanomedicine PLB-Cu@B-H [14]. Copyright 2025, Elsevier Ltd.

The nanocomplexes trigger Cu^{2+} release via high concentrations of GSH and acidic microenvironment in tumor cells. The released Cu^{2+} induce immunogenic death of tumor cells through multiple pathways, including cuproptosis, ferroptosis and necroptosis. This dual-response nanomaterial achieves precise targeted killing of tumor cells while activating the immune system and enhancing the antitumor efficacy. Liu et al. [100] combined functional peptides dually responsive to MMPs and ROS with photosensitizers and immune agonists, and utilized the masking and targeting effects of M1 macrophages to enhance drug accumulation, penetration, and cellular uptake in tumors. This is attributed to the fact that high levels of MMP and ROS promote size changes in nanosystems, a process that achieves deep tumor penetration and efficient uptake, leading to synergistic treatment of OSCC by PDT and tumor immunotherapy, which combine to produce significant therapeutic effects. These studies demonstrate that multi-stimuli-responsive nanomaterials can precisely recognize the characteristics of the TME and achieve functional regulation. This not only provides efficient and precise strategic support for synergistic tumor therapy but also exhibits broad potential for clinical therapy.

TME-responsive materials: features and outlook

Table 3 lists the advantages and limitations of different TME-responsive DDSs. TME-responsive nanomaterials hold great promise in precision DDSs; however, the clinical translation still faces challenges. The TME exhibits significant inter-patient, intratumoral, and spatiotemporal heterogeneity, leading to substantial variations in responsive signals across different patients, distinct regions within the same tumor, and different disease stages. Consequently, single-response mechanisms struggle to achieve stable and predictable precise triggering. Specifically, GSH-responsive materials are constrained by a dual dilemma: basal GSH levels in normal tissues can induce premature carrier degradation and off-

target toxicity [33,35]; moreover, intratumoral GSH concentrations not only vary significantly among different patients but also exhibit highly heterogeneous spatial distribution within the same tumor [34,39], resulting in unstable response efficiency. pH-responsive materials face a similar challenge: the pH gradient between solid tumors and normal tissues is inherently limited, and the pronounced spatiotemporal heterogeneity of intratumoral acidity across different regions and disease progression stages [50,53] further accentuates the risks of nonspecific responses and off-target toxicity. ROS-responsive materials are additionally compromised by the significant gradient heterogeneity of hypoxia within solid tumors, which further suppresses ROS generation and diminishes triggering efficacy, beyond the interference from basal ROS levels in normal tissues. Enzyme-responsive materials, in turn, suffer from compromised response reliability due to the significant heterogeneity in the expression of target enzymes such as MMPs across different patients, tumor types, and intratumoral regions, coupled with the potential for nonspecific degradation induced by low levels of homologous enzymes in normal tissues. Moreover, the fabrication of such materials involves intricate and delicate procedures, with poor batch-to-batch reproducibility and technical barriers to scalable manufacturing. The emergence of multi-responsive materials is precisely intended to overcome the failure risk of single systems in heterogeneous tumors and simultaneously activate multimodal synergistic therapy; however, the introduction of multiple responsive units increases the structural complexity of carriers, potentially compromising biocompatibility and causing temporal asynchrony in responses [99]. Furthermore, multi-component systems exhibit poor batch-to-batch reproducibility and high preparation costs, and existing studies generally lack systematic evaluation of their in vivo metabolic behavior and long-term biosafety, all of which further constrain clinical translation. Therefore, TME-responsive DDSs currently remain predominantly at the preclinical stage.

Table 3. Comparison of different response strategies (GSH, pH, ROS, enzymes and multi-response DDSs)

Classification	Advantages	Limitations
GSH	High specificity; disulfide bond responsive cleavage	High GSH in normal tissues triggers nonspecific responses
pH	Widely applicable across diverse solid tumor types	Similar acidic profile in inflamed tissues diminishes response selectivity
ROS	Sustainable ROS amplification through feedback-loop engineering improves treatment efficacy	Limited dose window; prone to scavenging by elevated tumor antioxidants
enzyme	High sensitivity; rapid response and release at low enzyme concentrations	Complex preparation processes and high synthesis costs
multi-responsive	Multi-stimulus synergistic triggering	Complex fabrication; undefined metabolic fate; long-term biosafety unverified

Future research should take tumor heterogeneity as the design starting point, commit to the rational simplification of carrier structures and the precise optimization of multi-responsive synergistic activation mechanisms, and establish standardized evaluation systems encompassing multiple heterogeneous tumor models while developing scalable manufacturing processes, thereby promoting the clinical translation of such materials toward personalized and predictable DDS. Concurrently, regulatory agencies should assume a pivotal role in formulating clinical standards and establishing rigorous efficacy evaluation protocols for TME-responsive nanomaterials.

CONCLUSION

This study explores the application of DDSs that can respond to different key components in the TME of OSCC (such as acidic pH, high concentration of GSH, ROS, overexpressed MMPs, etc.) in cancer treatment. Based on the unique biological properties of the TME, intelligent DDSs can be constructed via nanotechnology. In terms of passive targeting, the enhanced permeability and retention (EPR) effect serves as the fundamental mechanism for nanoparticle drug delivery in solid tumors. The leaky, defective vessels formed by rapid angiogenesis in solid tumors, coupled with impaired lymphatic drainage, collectively give rise to the enhanced permeability and retention effect, which can increase macromolecular enrichment in the tumor microenvironment by up to 70-fold [101]. However, passive targeting has significant limitations: it cannot distinguish between healthy and diseased tissues, results in insufficient tumor accumulation, and exhibits marked intratumoral, intertumoral, and interindividual heterogeneity. The diversity of vascular architecture and TME parameters further contribute to the high variability of EPR-mediated nanoparticle accumulation [101-102]. Therefore, active targeting strategies have been widely adopted in the design of OSCC drug delivery systems, wherein tumor-specific ligand modifications (such as folate modification) enhance tumor cell recognition and binding capacity to compensate for the inherent deficiencies of the EPR effect. Additionally, DDSs can trigger controlled drug release under the stimulation of TME-specific signals (e.g., pH-sensitive nanocarriers undergo structural dissociation in an acidic environment, and GSH-responsive carriers release drugs through disulfide bond cleavage). This precise delivery mode not only significantly enhances the anti-tumor efficacy but also effectively reduces the systemic toxic reactions

caused by the non-specific distribution of drugs in traditional treatment methods such as chemotherapy and radiotherapy. It provides new technical support and research directions for the precise treatment of OSCC, and is expected to promote the transformation of OSCC treatment towards "individualized precision treatment".

However, despite the numerous breakthroughs achieved by TME-responsive DDSs in the field of OSCC treatment, there are still many core challenges that urgently need to be addressed, which seriously hinder their translation from basic research to clinical practice: (1) The long-term biosafety and potential toxic and side effects of nanomaterials remain unclear. Most nanocarriers (such as metal-based nanomaterials) may cause problems such as oxidative stress, inflammatory responses, and organ accumulation damage due to their long-term retention in the body. Moreover, their potential long-term effects, such as immunogenicity and genotoxicity, still lack systematic long-term animal experimental verification. (2) The stability and metabolic pathways of DDSs in complex physiological environments still need to be further explored. After entering the body, nanocarriers have to go through multiple barriers such as maintaining blood circulation, evading phagocytosis by the mononuclear phagocyte system (MPS), penetrating tumor blood vessel walls and the dense tumor ECM. During this process, they are prone to aggregation, degradation or off-target effects, and key information such as their in vivo metabolic pathways, excretion methods and clearance efficiency has not yet been fully clarified. (3) The heterogeneity of the TME can lead to differences in responsiveness, and there is still room for improvement in aspects such as response specificity and sensitivity. Significant differences exist in TME components among different OSCC patients and even among different tumor sites of the same patient, resulting in uneven response effects of DDSs. Meanwhile, the existing response mechanisms are susceptible to slight interference from the microenvironment of normal tissues, with problems such as insufficient response specificity, high stimulation threshold, and incomplete drug release. (4) The synergistic mechanism of multi-stimuli responsiveness still needs to be broken through. Single-stimuli responsive systems are difficult to cope with the complex and variable TME. Although some studies have attempted to construct multi-stimuli responsive systems such as pH/GSH and MMP/ROS, most of these systems only achieve simple superposition of different response modules, fail to realize the synergistic effect of each

response mechanism, and thus are difficult to accurately match the dynamic changes of the TME. In addition, the complex preparation process, high production cost and difficult standardization of large-scale production of DDSs have also caused serious obstacles to its clinical transformation. The existing preparation methods in the laboratory stage are mostly small batch fine operations, which are difficult to achieve large-scale scale amplification. Moreover, the particle size, morphology, drug loading and other key indicators of different batches of products are prone to fluctuation, and there is a lack of unified quality control standards and industrialized production technology. In conclusion, to overcome existing limitations and fully exploit the potential of TME-responsive drug delivery platforms, future research should focus on: (1) harnessing artificial intelligence and tumor heterogeneity data to enable precision nanocarrier design for personalized nanomedicine; (2) integrating biomimetic materials with nanocarriers to enhance their targeting ability and biocompatibility; and (3) developing imaging-guided, smart-responsive nanomedicine platforms to achieve theranostic integration. Additional efforts will be required in the future to accelerate the clinical translation of these DDSs.

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CONFLICTS OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHORSHIP CONTRIBUTIONS

M. W: Writing-original draft, Investigation, Formal analysis. **X. H:** Writing-review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **J. H:** Methodology, Investigation. **Y. G:** Formal analysis, Investigation. **Y. M:** Writing-review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

AI STATEMENT

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

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