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Design Strategies of Hypoxia-Responsive Nanocarriers for Targeted Drug Delivery in the Tumor Microenvironment

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Abstract. Hypoxia is one of the hallmark features of solid tumors, and it leads to treatment resistance, metastasis, and immunosuppression. While physiological hypoxic microenvironments also exist in normal tissues, tumor hypoxia has more severe, longer-lasting, and higher spatial heterogeneity pathological characteristics. This important feature makes it an attractive trigger for nanomedicine drug delivery systems, and hypoxia-responsive nanocarriers are being developed as a preclinical strategy to utilize this property for the controlled release of drugs at specific spatiotemporal locations. This review focuses on four dimensions: hypoxia-responsive chemical groups and their nano-carriers, hypoxia-activated prodrugs, oxygen supply and oxygen-generating systems, and multi-stimuli integration, which mainly explores design strategies and representative cases of hypoxia-responsive nanocarriers for drug delivery, comparing their mechanisms, advantages, and limitations. The core conclusion is that the rational design of hypoxia-responsive nanocarriers should match the pathological characteristics of hypoxia in the tumor microenvironment, while being supplemented by multi-stimulus integration and dynamic penetration strategies. Key design principles and current transformation challenges were summarized in the end, aimed to provide guidance for the future design and application of hypoxia-targeted nanomedicines.

Keywords: tumor hypoxia, nanocarriers, targeted drug delivery, TME

1. Introduction

1.1. Challenges in cancer therapy currently

In recent years, cancer treatment has made numerous breakthrough advances in chemotherapy regimens, radiation therapy protocols, and immunotherapy strategies, but challenges such as drug resistance, systemic toxicity, and insufficient tumor selectivity still exist, which prevent a significant portion of patients from achieving effective clinical outcomes [1, 2]. Traditional cytotoxic chemotherapy and radiotherapy often have multiple different mechanisms of action. Overall, Chemotherapy primarily relies on differences in cell proliferation rates, while radiotherapy places greater emphasis on oxygen content. However, the tumor microenvironment (TME), particularly the hypoxic tumor environment, forms physical and biochemical barriers in the body. This makes it difficult to distinguish between malignant and healthy tissues during treatment, hinders effective

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drug delivery and therapeutic response, resulting in a narrow therapeutic window and suboptimal treatment outcomes.

1.2. TME

TME is a complex ecosystem composed of cellular components such as cancer cells, stromal cells, and immune cells, as well as non-cellular components including the extracellular matrix (ECM), chemokines, and metabolites [3, 4]. The normal tissue microenvironment (NTE) can maintain immune homeostasis and restrict abnormal cell proliferation. In contrast, TME reshapes the local environment around cancer cells through pathways such as abnormal angiogenesis, chronic hypoxia, and excessive ECM deposition. These features are not merely the result of tumor growth but also important factors that further support tumor growth, and this positive feedback loop constitutes one of the core obstacles in cancer treatment.

Among the various physical and chemical abnormalities in TME, hypoxia plays a critical role particularly. It is associated with poor prognosis and treatment resistance in various cancer types, making this pathological feature an important source of inspiration and trigger for designing intelligent drug delivery systems (DDS). Although physiological hypoxic microenvironments can also exist in some normal tissues, their regulatory mechanisms and resulting effects are very different from those of tumor hypoxia, which state is more severe, persistent, and spatially heterogeneous.

1.3. Nanotechnology-enabled drug delivery

Nanotechnology is gradually advancing DDS by improving solubility, extending circulation time, and enhancing tumor accumulation through the utilization of the enhanced permeability and retention effect (EPR effect) [5]. Traditional nanocarriers mainly rely on passive diffusion in the body, lacking precise control over the location and timing of drug release, which directly affects the distribution of drugs in the body and therapeutic efficacy. As a result, the field is gradually shifting from empirical trial-and-error formulations to more rational design strategies.

The development of stimulus-responsive nanocarriers holds significant representative significance and promising prospects. By integrating molecular switches that respond to specific internal or external signals, they can achieve spatiotemporal control over drug release in the body. There are various endogenous stimuli in TME, among which hypoxia, due to its severity, persistence, and spatial heterogeneity in solid tumors, holds special appeal and inspiration for the design of such molecular switches.

1.4. Scope and purpose of this review

This review focuses on the design strategies for hypoxia-responsive nano-carriers for targeted drug delivery. After exploring the characteristics of hypoxic tumor microenvironments and the advantages of stimulable nanocarriers, this text discusses hypoxia-responsive nanocarriers for drug delivery from multiple aspects, which include nanocarriers with direct integration of hypoxia-responsive elements, as well as non-strictly hypoxia-responsive nanocarriers. This encompasses the delivery of hypoxia-activated prodrugs (HAPs) directly related to hypoxia-targeting, oxygen supply or oxygen-generating systems, and their combined applications with hypoxia-responsive carriers. Additionally, it covers design strategies, representative cases, and remodeling of TME brought about by enhanced penetration strategies.

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While some reviews have provided broad overviews of tumor microenvironment-responsive systems, there remains a relatively limited comparative analysis focused on hypoxia-specific design strategies, particularly those related to nanocarriers. This paper primarily provides theoretical guidance for the design of hypoxia-targeted nanomedicines by conducting comparative analysis across dimensions such as chemical principles and triggering mechanisms, multi-stimulus integration, and dynamic penetration, addressing current challenges and offers prospects to fill the gap in this field.

2. Hypoxia in TME

2.1. Origins, molecular hallmarks and tumor-promoting effects

Hypoxia, or low oxygen availability in tissue, is one of the common characteristics of TME and a hallmark of 50–60% of solid tumors [6]. Different types of tumors and measurement methods may define hypoxia differently. For example, regarding radiobiological hypoxia that occurs locally in most advanced tumors, the prevailing current view generally considers a $pO2 \leq 2.5$ mmHg as the hypoxic level at which significant radiation resistance is observed, but it may also fluctuate due to the type of organization and cellular composition, as well as the spatiotemporal heterogeneity of oxygen concentration in the tumor [7]. It primarily attributed to the imbalance between rapid proliferation of tumor cells and disordered angiogenesis, and the infiltration of immune cells as well. Cancer cells need to be able to adapt and survive in low-oxygen environments, so that the majority of tumor cells activates various molecular pathways related to hypoxia for adapting to the hypoxic environment, promoting their growth, survival, proliferation, and metastasis. Hypoxia-inducible factor 1-alpha (HIF-1α) is one of the most important transcription factors at the forefront of the cellular response to hypoxia. In hypoxic conditions, HIF-1α would be activated and induces the expression of various substances such as Twist, Snail, MMPs, GLUT1 and so on, facilitating the adaptation of cancer cells to low oxygen and nutrient availability [8].

Hypoxia in TME contributes significantly to the tumor burden and it is a barrier of the tumor treating, since it is closely associated with tumor invasion and metastasis, metabolic reprogramming, immune suppression, and angiogenesis [9]. However, it is also a great opportunity to develop therapeutic strategies for the intricate microenvironment of hypoxic tumors.

2.2. Hypoxia as a therapeutic trigger for smart nanocarriers

Physiological hypoxia can also exist in normal tissues. It is transient and controlled, and is generally regulated according to physiological conditions. While pathological hypoxia, one of the characteristics of solid tumors, is often persistent and severe, which contributes not only to tumor growth but also to therapy effectiveness, leading to a most malignant phenotype and a poor patient prognosis [10]. Due to the disordered blood vessel structure, the natural diffusion of oxygen from the closest blood vessel is prevented so that most tumors larger than 1 mm3 contain regions of hypoxia. It contributes significantly to tumors burden, approximately 20–30 % of treatment failures in radiotherapy and chemotherapy (CT) are attributed to tumor hypoxia [11]. Therefore, targeting the hypoxic response is a major issue that is urgently needed to be addressed in clinical practice at present, and the hypoxic characteristics of tumors also provide a therapeutic window for hypoxia-responsive nanocarriers.

Under hypoxic conditions, a reduced pH and the over-expression of several reductases, like azoreductase (AZR), are developed in TME. The reducing properties of this environment can be

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selectively responsive to specific chemical groups, such as azobenzene (Azo), nitroimidazole. For example, AZR-mediated reduction process is strongly determined by oxygen availability; only when low oxygen concentrations are present, azo compounds suffer an irreversible reductive breakdown of the azo bond [10].

Currently, cancer treatment using hypoxic environments is primarily achieved through two different approaches. One method involves the use of HAPs; the other entails developing new nanocarriers based on hypoxic conditions [12]. HAPs are bioreducible prodrugs that undergo selective activation in hypoxic regions by redox enzymes. This activation is at the organizational level, hypoxia-dependent rather than cell-specific, so some HAPs can still be partially reduced in normoxic tissues, leading to off-target toxicity. While this strategy can enrich active drugs in hypoxic tumor regions, it does not guarantee a reduction in systemic toxicity on its own. Moreover, their low extravasation remains a significant challenge in clinical trials, making the latter study of the nanocarrier delivery systems highly important. Nanomaterials can also serve as multifunctional diagnostic and therapeutic platforms for tumor imaging and treatment. Research has found that TME is highly sensitive to nanomaterials such as MnO2, which have already been applied in the biomedical field [13], further demonstrating the possibility of research and development in this area.

Based on the above, developing nanocarriers that utilize hypoxia signals to achieve precise drug release is an inevitable trend. A systematic organization and comparative analysis of the relevant design strategies will be conducted next.

3. Stimuli-responsive nanocarriers

Targeted drug delivery technology has evolved from a simple concept of delivering drugs to target tissues into a complex therapeutic strategy involving control over the spatial, temporal, and biological aspects of the drug release process. The introduction of nanocarriers can further enhance drug stability, alter its pharmacokinetic properties, extend the drug's circulation time in the body, increase drug solubility, protect fragile therapeutic molecules, and modify drug tissue distribution [14].

However, first-generation nanomedicine primarily relied on passive targeting mechanisms, which achieved targeting of tumor cells through the enhanced permeability and EPR effect. Due to the heterogeneity of human tumors in multiple aspects, nano-carrier strategies with universal applicability have significant uncertainty in their clinical efficacy. To overcome these limitations, research on stimulus-responsive nanocarriers has gradually deepened in recent years.

3.1. Fundamental principles

Stimulus-responsive nanocarriers are nanoscale DDS that remain relatively stable during circulation in the bloodstream and can release their loaded drugs upon exposure to specific biochemical or physical triggers. Stimulus response systems can usually be divided into endogenous stimuli and exogenous stimuli based on the triggering factors of the activation carrier. Endogenous stimulation refers to the intrinsic signaling of TME, including pH, glutathione (GSH), hypoxia, etc., while the latter mainly consists of externally applied signals such as light, heat, and magnetic fields [14]. Liposomes, polymer nanoparticles and hydrogels are common carrier materials.

Traditional nanocarriers often achieve passive targeting through EPR effect, showing the disadvantage of being unable to be precisely controlled. Stimulus responsive carriers can add special control switches that help to precisely control drug release, thereby increasing tumor cell uptake and reducing damage to normal cells caused by inaccurate release. This spatiotemporal specificity of

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stimulus responsive carriers, which precisely control drug release, makes them of significant research value. However, this technology still faces many problems such as high synthesis complexity, potential instability of responsive groups, and additional conversion barriers.

3.2. Hypoxia-responsive nanocarriers

Zhou Xuewu et al. classified hypoxia targeted nanomedicine delivery strategies into those that utilize hypoxia characteristics, alleviate hypoxia, reshape the hypoxic tumor microenvironment, and actively target hypoxic areas [15]. Based on the consideration of this classification, we will start from the promising carrier design concept of hypoxia and explore the design strategies of hypoxia responsive nanocarriers from multiple aspects, hoping to provide some guidance and reference for this field.

3.2.1. Hypoxia-labile chemical moieties

In hypoxic environments, the accumulation of a large amount of NADPH and overexpression of reductase make the TME reducible. Oxygen-sensitive groups refer to chemical groups that undergo selective reduction under such conditions, a property that can be utilized to trigger drug release from nanocarriers.

Azo, 2-nitroimidazole, nitrobenzyl alcohol, quinone derivatives, etc. are currently widely used in clinical practice. Among them, Azo is one of the most commonly used and extensively studied chemical groups [16]. Under anaerobic conditions, the N=N double bond of Azo is reduced and broken by azo reductase, allowing it to act as a linker to block the pores of nanocarriers such as mesoporous silica. 2-nitroimidazole was first used to synthesize hypoxia responsive polymers due to the reduction of nitro ($-NO_2$) to amino ($-NH_2$) by nitroreductase under hypoxic conditions, which alters the hydrophilic lipophilic balance of the molecule. Compared with Azo and nitroimidazole, the application range of other functional groups is relatively small.

Azobenzene-gated mesoporous silica nanoparticles (MSNs) in azobenzene-gated systems are highly representative. The design concept involves using MSNs as carriers to load chemotherapeutic drugs (such as doxorubicin, Dox), with Azo serving as a gatekeeper to block mesoporous channels. In a hypoxic TME, Azo is cleaved by overexpressed azoreductase enzymes, leading to Azo detachment, pore opening, and subsequent Dox release. Studies have shown that under hypoxic conditions, the release of Dox in A549 lung cancer cells is promoted, which in turn significantly enhances its cytotoxicity, playing an important role in selectively killing hypoxic tumors [10].

The core feature of such strategies is a direct causal relationship between drug release and hypoxia signals, and they rely on precise chemical synthesis and group modification.

3.2.2. HAPs

Unlike nanocarriers, HAPs themselves are not delivery vehicles, they are a class of small-molecule bioreductive prodrugs that are selectively activated by reductases in hypoxic tumor microenvironments. These reductases reduce the prodrugs to generate cytotoxic active drugs, which selectively kill local cancer cells [9].

Tirapazamine (TPZ) is one of the earliest hypoxia-selective drugs and the first hypoxia-activated prodrug to enter clinical trials. It is an N-oxide analog that, under hypoxic conditions, undergoes one-electron reduction by NADPH-cytochrome P450 reductase (CYPOR) to generate TPZ radicals, which then induce single-strand and double-strand DNA breaks, leading to cell death. As of now,

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TPZ has advanced to Phase II/III clinical trials in multiple solid tumors, including head and neck cancer, ovarian cancer, and non-small cell lung cancer [9].

Evofosfamide is a nitro-containing HAP with 270 times higher selectivity for hypoxia than normoxia. It has advanced to Phase III clinical trials and is one of the most clinically mature HAPs.PR-104 is a phosphate ester prodrug that can be rapidly converted into its active form PR-104A in the body. Under hypoxic conditions, it is reduced by nitroreductase to a highly potent cytotoxic nitrogen mustard, which induces interstrand DNA cross-linking. Clinical trials are now being conducted in leukemia and various solid tumors. Molecularly targeted HAPs such as TH-4000 (tarloxotinib) are also in clinical development.

HAPs have pharmacokinetic defects such as low extravascular transport, rapid in vivo clearance, and insufficient tumor accumulation. Taking TPZ as an example, although it showed significant preclinical efficacy, clinical trials of free TPZ failed to significantly improve overall survival, partly due to its toxicity and limited tumor delivery efficiency. The design of nanocarriers helps further develop drug delivery platforms, which can address such defects to some extent by extending circulation time, enhancing tumor-targeted accumulation, or controlling release. Au-PEI-Azo-mPEG nanoparticles loaded with TPZ (APAP NPs) are a typical example. Its structure is centered on gold nanoparticles (AuNPs), with polyethyleneimine (PEI) coated on the surface, and further connected to an mPEG shell via Azo. In the hypoxic tumor microenvironment, Azo is reduced and cleaved, leading to the shedding of the PEG shell and thereby exposing TPZ. Furthermore, TPZ will be further reduced to its active form due to the lack of Oxygen. Experimental data showed that APAP NPs reduced the IC_{50} of TPZ to 7.46 μg/mL under hypoxic conditions (24 hours), increased cellular uptake by approximately 100-fold, and could completely disrupt MCF-7 tumor spheroids within 72 hours [17]. The generation of these results is closely tied to the design of the carriers, so the extent of improvement for each parameter in nanocarrier delivery must be evaluated on a case-by-case basis.

The core characteristic of such strategies is that the drugs themselves have hypoxia selectivity, and they are characterized by dependence on tumor uptake efficiency and limited efficacy as monotherapies.

3.2.3. Oxygen-delivering and oxygen-generating systems

Unlike the strategies in 3.2.1 and 3.2.2 that use hypoxia as a trigger signal, the core logic of oxygen delivery and generation systems is to actively alleviate hypoxia itself, i.e., to improve tumor oxygenation by directly delivering oxygen or generating oxygen in situ within the tumor. The relationship between the two is not competitive; instead, they complement each other. Alleviating hypoxia can reduce HIF-1α and reverse multiple treatment resistance mechanisms, thereby creating favorable conditions for other treatments such as PDT, radiotherapy, and chemotherapy [18].

Current research primarily delivers oxygen directly to tumors using two major categories of nanocarriers: perfluorocarbons (PFCs) and hemoglobin-based oxygen carriers (HBOCs). PFCs have extremely high oxygen solubility and can be formulated into nanodroplets or nanoemulsions to carry and release oxygen. Experimental results show that the droplet can effectively penetrate the core of tumor spheroids, significantly reduce the expression of HIF-1α and HIF-2α, and achieve sustained hypoxia relief for up to 3 hours [19]. HBOCs encapsulate hemoglobin in nanoparticles to transport oxygen and show potential applications in tumor radiotherapy and chemotherapy.

In addition to exogenous oxygen delivery, endogenous substrates (H_2O_2) in tumors can also be utilized to generate in situ oxygen, which has many potential advantages. It does not require external oxygen loading, can simultaneously consume hydrogen peroxide within tumors, and based on

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certain carriers, can also function as an oxygen generator. Common carriers include MnO_2 nanomaterials with peroxidase-like activity that catalyze the decomposition of excess H_2O_2 in TME to generate O_2, CaO_2 nanoparticles that release oxygen and H_2O_2 in an acidic tumor microenvironment while producing calcium ions, as well as nanozymes such as CeO_2 (cerium dioxide).

Relieving hypoxia can reduce HIF-1α expression, reverse multiple treatment resistance mechanisms, making this strategy particularly suitable for combination with oxygen-dependent therapies. However, due to the varying availability of endogenous hydrogen peroxide across different tumor types and regions within the same tumor, the therapeutic benefits of this approach are context-dependent and require validation in relevant tumor models.

3.2.4. Comparative analysis and strategy selection

A comparison of the several strategies mentioned earlier yields Table 1 as follows.

Table 1. The comparative analysis of the three hypoxia-responsive strategies

Dimensions	Hypoxia-Labile Moieties	HAPs	O_2 Delivery/Generation
Core Mechanism	Hypoxia environment is reductive → Chemical bond changes→ Changes in carrier structure → drug release	Hypoxia-reduction activation of prodrug molecules → Generation of active drugs	Delivery/Generation of O_2 → Alleviation of hypoxia → Reduction of relevant factors (like HIF-1α)
Key Advantages	Precise controlled release; Strong platform compatibility; Modular design capability	Part entered clinical trials; Selective cytotoxicity	Indirectly improve multiple treatments; Great potential for combination with PDT/radiation therapy
Limitations	Synthetic chemical dependency and complexity; Unknown safety of metabolites; Tumor heterogeneity	Depends on tumor uptake efficiency; Limited efficacy as a single agent; Potential toxicity	Oxygen supply is transient; Reliance on endogenous H_2O_2; Poor efficacy when used alone
Applications	Precise control of nano chemotherapy drugs	Combination therapy with radiotherapy and chemotherapy	Therapy combined with oxygen

The low oxygen sensitive groups and HAPs strategies in Table 1 both utilize low oxygen as a direct trigger signal for drug release or activation, while the third strategy is different in that it specifically uses low oxygen as an intervention for cancer treatment. Regardless of how hypoxia is utilized, these strategies are not mutually exclusive. For example, HAPs can be co delivered with oxygen producing manganese dioxide nanoparticles to sequentially regulate and utilize hypoxic conditions.

3.3. Multi-stimuli responsive systems

The basic principle of designing hypoxia responsive nanocarriers is to utilize the unique reducing chemical environment of tumor hypoxic regions and achieve precise drug delivery through structural

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changes of specific chemical groups. Due to the varying degrees of hypoxia in different regions of the tumor, oxygen levels also fluctuate over time, exhibiting spatial heterogeneity and temporal dynamics. The three strategies listed in Table 1 have common limitations - incomplete drug release or low efficacy in areas with moderate or high hypoxia.

Integrating multiple stimuli, such as pH, GSH, or enzymes, into a single nanocarrier platform for logic gate activation, to trigger drug release by one or more tumor microenvironment signals, is one of the directions that can be explored in this field in the future. This method can maximize the specificity of drug release and reduce non targeted release, to some extent breaking through the limitations of a single stimulus response system.

The multi stimulus response system is divided into dual response and triple response systems. Common dual-response combinations include hypoxia/pH, hypoxia/GSH, and hypoxia/enzyme. For example, hypoxia/pH dual-responsive covalent organic framework (COF) nanocarriers (COF-PBA) integrate acid-sensitive and hypoxia-responsive sites to enhance drug penetration, while hypoxia/GSH dual-responsive cross-linked polymer nanoparticles (CLPNPs) trigger drug release upon exposure to either stimulus [20, 21]. As for triple-response systems such as hypoxia/reactive oxygen species/pH responsive metal-organic frameworks (MOFs), they have more complex cascades or sequential requirements, necessitating stimuli to appear in a specific order to exert their intended functions. The three response system is still in the early exploration stage [22].

3.4. Dynamic targeting and deep penetration strategies

How to make nanocarriers penetrate the tumor stroma and ultimately reach the hypoxic area is also a major challenge in hypoxia targeted nanotherapy. To overcome this physical barrier, existing research mainly considers three strategies.

3.4.1. Charge-reversal nanocarriers

Nanocarriers with a negative surface charge are beneficial for extending circulation time in the bloodstream but are unfavorable for uptake by cell membranes that also carry a negative charge. While positive charges help cells take up substances but are also more easily cleared by the immune system. In order to ensure sufficient cellular uptake and evade rapid clearance by the immune system, it is necessary to design nanocarriers that can achieve charge reversal in the tumor microenvironment. This type of nanocarrier can maintain a negative charge in the blood to prolong circulation time, and when it reaches the acidic tumor microenvironment, it can quickly reverse to a positive charge to promote uptake by cancer cells.

Researchers have found that acid sensitive amide or ester bonds can be used to shield negatively charged groups, which break under acidic conditions (pH 6.5-6.8) in TME, exposing positively charged groups. PH responsive charge reversal nanoparticles have been shown to transform from -15 mV to+20 mV in acidic tumor microenvironments, increasing extracellular uptake efficiency by about three times [23]. This provides an important design concept for nanomedicine to cross physical barriers and exert efficacy.

3.4.2. Size-transformable carrier systems

The size of nanoparticles can affect the circulation speed of drugs in the blood and tumor penetration ability. Under normal circumstances, small-sized nanoparticles (about 20-50 nanometers) have strong diffusivity and penetration ability, and are easily removed quickly through renal filtration;

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The diffusion of large-sized nanoparticles (about 100 nanometers) is relatively limited, making it difficult to penetrate the dense tumor ECM and high interstitial pressure areas. Therefore, they are mainly cleared by being taken up by the reticuloendothelial system (RES/MPS). This process is also influenced by factors such as surface chemical properties.

To balance the circulation speed and permeability, the design of nanocarriers can be approached from the perspective of size shrinkage occurring in TME. The design of the system needs to meet the requirements of maintaining a larger size during circulation and responding to TME signals to shrink to a smaller size after reaching the tumor, while ensuring reduced renal clearance and enhanced permeability of the reticuloendothelial system (MPS) uptake. It was found that under the pH 6.5 condition, the pH responsive nano gel contracted from about 120 nm to about 30 nm, and the penetration depth in the three-dimensional tumor sphere model increased by about twice [24]. The construction of nanoparticles with pH responsive or enzyme responsive crosslinking groups makes it possible for drugs to shrink in size in TME. One of the directions that can be explored in the future is how to improve the concealment in the loop process to avoid premature clearance.

3.4.3. Stimuli-regulated dynamic ligand presentation

To enhance the specific recognition and uptake of tumor cells by nanocarriers, targeting ligands can be considered in the design. But it should also be noted that ligands should not be exposed to the bloodstream too early, otherwise it may lead to non-specific uptake of nanocarriers by normal tissues or recognition and clearance by the immune system, thus failing to achieve good therapeutic effects.

Designing a 'shieled/unshielded' ligand presentation system allows ligands to be 'shielded' (in inactive state) by inert protecting groups or PEG chains in the bloodstream, and then 'unshielded' (activated state) upon reaching the TME in response to hypoxia, pH, or enzymatic signals, exposing the ligand to mediate active targeting. PEG shielding technology sensitive to acids has been used to mask targeting ligands such as RGD peptides. In an acidic tumor microenvironment, the PEG corona is cleaved, thereby exposing ligands to mediate active recognition and uptake of tumor cells.

4. TME remodeling via hypoxia-responsive nanocarriers

The design of hypoxia-responsive nanocarriers not only aids in the precise and efficient delivery of drugs but also plays an important role in reshaping the TME. This remodeling helps to reverse, to some extent, immune suppression and abnormal angiogenesis, or further establish a positive feedback loop to enhance drug delivery efficacy.

4.1. Alleviating hypoxia

Hypoxic conditions upregulate PD-L1 expression on the surface of tumor cells via HIF-1α, thereby promoting the recruitment and functional polarization of immunosuppressive cells (TAMs, MDSCs, Tregs), which further contributes to the construction of an immunosuppressive TME. Hypoxia-responsive nanocarriers (such as MnO_2 nanoplatforms) can reduce HIF-1α levels by delivering oxygen or generating oxygen in situ [13]. The downregulation of HIF-1 α can cause a series of changes. The reduction of PD-L1 expression alleviates immune suppression; Tumor associated macrophages (TAMs) can polarize from the pro tumor M2 phenotype to the anti-tumor M1 phenotype, increasing the infiltration of $CD8^+$ T cells [8], and so on. These are expected to enhance

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the efficacy of immune checkpoint inhibitors, laying a theoretical foundation for the development of combination therapy.

4.2. Vascular normalization and enhanced drug delivery

Under hypoxic conditions, vascular endothelial growth factor (VEGF) is overexpressed, leading to abnormal tumor vascular structure, manifested as tortuous blood vessels, leakage, and disrupted branching. The utilization of hypoxia responsive nanocarriers can alleviate the hypoxic environment of tumors to a certain extent, thereby downregulating VEGF expression, reducing leakage, and improving vascular structure [25]. The normalization of vascular structure can further improve tumor perfusion and oxygenation, promote the delivery of nanocarriers, and facilitate the rational distribution of drugs.

4.3. The dual role of hypoxia-responsive nanocarriers

Hypoxia responsive nanocarriers play a dual role in intelligent delivery and regulation of TME. It can not only accurately release drugs in hypoxic areas, but also alleviate hypoxia, reverse immune suppression, and normalize blood vessels. And these two functions work together and complement each other, relieving hypoxia can improve drug delivery efficiency, while more efficient delivery further enhances hypoxia relief, ultimately forming a positive feedback loop that amplifies therapeutic gains [26]. This characteristic gives hypoxia responsive nanocarriers unique advantages and promising development prospects in combination therapy, but there are still several challenges to be addressed in their clinical translation.

5. Conclusion

The design strategy discussed in this article needs to follow a series of key principles. For example, when selecting a low oxygen responsive chemical group, consideration should be given to whether the drug type matches the expected release curve, and the design should take into account the pathological characteristics of tumor hypoxia, not relying solely on the presence of a low oxygen environment. Physiological low oxygen environments also exist in normal tissues, and targeting this low oxygen environment should be avoided to prevent other consequences. By designing dynamic targeting and penetration strategies, drug delivery to the hypoxic core region can overcome physical barriers, while also considering the integration of multiple stimuli to reduce the limitations of a single stimulus response system. In practical design, production, and application, it is necessary to consider these in conjunction with existing transformation challenges.

At present, an important challenge facing the clinical translation of hypoxia responsive nanocarriers is the spatiotemporal heterogeneity of tumor hypoxia, which limits the limitations of single stimulus or fixed threshold response systems and requires increased exploration of multi stimulus response systems. In addition, the physiological hypoxic microenvironment in normal tissues may also lead to non targeted activation of carriers, and the development of multi signal regulatory systems may help reduce this risk. The current preclinical models are difficult to perfectly replicate the hypoxic structure of human tumors, which limits the predictive value of animal research. Further exploration is needed to improve the accuracy of preclinical trial predictions and the reliability of experimental results while ensuring low costs. Although various HAPs have entered the clinical trial stage, nanocarriers that respond to hypoxia have not yet reached the clinical evaluation stage, and there is still a long way to go to bridge this gap.

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