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Research Progress and Optimization Strategies for Tumor-Targeted Polymer-Based Nanodrug Delivery Systems

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Abstract

Malignant tumors exhibit significant cellular and tissue heterogeneity. Traditional chemotherapy drugs lack the ability to target tumors, and combined with the multiple physiological delivery barriers in tumor tissues, this often leads to systemic toxic side effects and multidrug resistance, thereby limiting the effectiveness of clinical treatment. Polymer nanomaterials, with their excellent biocompatibility and structural modifiability, have become important carriers for targeted drug delivery in oncology. This paper focuses on polymer-based nanodrug delivery systems, reviewing the mechanisms of action of mainstream targeting strategies—including passive targeting, active targeting, tumor microenvironment-responsive drug release, and cell membrane biomimicry—and analyzing key challenges in this field: individual heterogeneity in the EPR effect leads to insufficient tumor enrichment and penetration into deep tissues. The complex in vivo microenvironment can easily cause inactivation of active targeting ligands and masking of recognition sites by the protein corona. The high heterogeneity of tumors makes it difficult for most carriers to simultaneously target primary tumors, circulating tumor cells, and micrometastases. The complex synthesis processes, poor batch-to-batch stability, and lack of long-term safety data for multifunctional carriers hinder clinical translation. To address these delivery challenges, this paper systematically summarizes optimization strategies, including the regulation of carrier physicochemical parameters, multi-target active modification, multi-stimulus-responsive drug release, biomembrane-based camouflage, and standardization of preparation processes. Research indicates that a single targeting strategy still has inherent limitations. In the future, it will be necessary to promote carrier design that integrates multiple technologies, balancing targeting efficacy, biosafety, and scalability, to overcome biological barriers and industrialization challenges, thereby providing a theoretical reference for the development and clinical translation of novel polymeric nanocarriers for anticancer drug delivery.

Keywords

cancer therapy, polymeric nanocarriers, targeted delivery, nanomedicines, clinical translation

1. Introduction

Malignant tumors exhibit significant cellular and tissue heterogeneity. This heterogeneity directly leads to variations in tumor vascular characteristics, individual variability in the EPR effect, and uneven expression levels of cell surface targets. At the same time, there are significant differences in the biological characteristics among the primary tumor, circulating tumor cells, and micrometastases. The abnormal vascular structure of

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tumors, dense extracellular matrix, and complex microenvironment—including acidic and hypoxic conditions—collectively form multiple layers of continuous physiological delivery barriers that interfere with drug distribution and action within the tumor, posing a major challenge for clinical treatment. Traditional small-molecule chemotherapeutic agents lack tumor-targeting capabilities. Once introduced into the body, they readily cause damage to normal organs such as the bone marrow, liver, and kidneys, leading to severe toxic side effects. Furthermore, long-term use can induce multidrug resistance in tumors. Therefore, how to achieve selective tumor delivery, overcome the multiple consecutive delivery barriers in the drug transport chain, and ensure effective drug concentrations at the tumor site remains a core scientific problem urgently requiring resolution in anticancer drug delivery research. Polymer nanomaterials, with their modifiable structures and good biocompatibility, serve as the mainstream carriers for targeted drug delivery. Current research on nanocarriers has evolved from a stage focused solely on prolonging circulation and achieving passive targeting via the EPR effect in solid tumors to a multi-level, multi-pathway design approach that includes ligand-conjugated active targeting, microenvironment-sensitive controlled drug release, cell membrane mimicry, and synergistic therapy through the co-loading of multiple drugs. At present, PLGA, PEG, natural polysaccharides and other matrix materials are often used to construct nano-micelles and nanoparticles. Some of these systems have entered clinical trials, which has preliminarily confirmed the potential of macromolecular carriers for targeted delivery to tumors. However, there are still multiple bottlenecks in the complete delivery chain (such as circulation, enrichment, recognition, etc.) of existing targeted polymer delivery systems in vivo. The passive targeting effect is greatly affected by tumor stage and individual microenvironment differences, the tumor enrichment rate of nanoparticles is generally low, and penetration into deep tumor tissue is insufficient. Active targeting ligands are easily degraded by enzymes in vivo, and repeated administration can easily trigger immune clearance and weaken targeting specificity. Most carriers are designed to target only tumors in situ, which cannot simultaneously target circulating tumor cells and micrometastases, making it difficult to meet the treatment needs arising from tumor heterogeneity. Furthermore, the synthesis processes for multifunctional polymeric carriers are complex, and evaluation systems for mass-production stability and long-term in vivo safety remain incomplete, hindering the progress of clinical translation. Existing reviews primarily focus on single-function carriers or a single type of targeting strategy, lacking a comprehensive in vivo delivery perspective. Therefore, this paper summarizes the current state of the art in the targeted modification of polymeric nanocarriers, analyzes the inherent limitations of various targeting strategies, outlines approaches for optimizing targeting efficacy, and explores the industrialization bottlenecks and practical challenges facing this class of nanomedicines, thereby providing a theoretical reference for the development of novel, highly targeted polymeric delivery carriers [1-7].

2. Basic Overview of Polymer-Based Nanodelivery Systems

Polymer-based nanodelivery systems are drug carriers prepared using polymer materials as a matrix. Their particle sizes typically range from 10 to 1,000 nm, and they can load various therapeutic agents—such as chemotherapeutic drugs, proteins, and nucleic acids—through encapsulation, chemical bonding, or physical adsorption, thereby modifying the drugs' transport behavior within the body. The polymeric materials used to construct these carriers are primarily divided into two categories: synthetic polymers and natural polymers. Among synthetic polymers, PLGA (poly(lactic-co-glycolic acid)) exhibits good biodegradability, and its molecular weight can be readily controlled, and the polymer is amenable to chemical modification. PEG (polyethylene glycol) is generally not used as a carrier matrix to construct nanoparticles on its own. Rather, it is often introduced as a hydrophilic modifying chain segment on the carrier surface, where its hydrophilicity and molecular flexibility reduce nonspecific adsorption and prolong circulation time in vivo. Natural polysaccharides such as chitosan and hyaluronic acid exhibit good biocompatibility and are readily available as raw materials. Common forms of nanocarriers include polymer micelles, solid nanoparticles, and nanogels: micelles formed by the self-assembly of amphiphilic polymers rely on a hydrophobic core to load hydrophobic drugs. The drug-loading characteristics of solid nanoparticles and nanogels are jointly regulated by the type of polymer, microstructure, and the physicochemical properties of the drug. Among these, nanogels with a three-dimensional cross-linked structure swell upon contact with water, providing potential loading space for hydrophilic drugs. Following intravenous administration, polymeric nanocarriers must sequentially undergo a series of processes, including systemic circulation, accumulation and permeation into tumor tissue, cellular uptake, and intracellular drug release. Each of these stages significantly influences the final drug delivery efficiency. Based on these delivery processes, existing polymeric nanosystems primarily improve delivery

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efficiency at different stages by adjusting material composition, surface properties, and functional modifications. However, each stage remains constrained by corresponding physiological barriers and the inherent properties of the materials themselves. The following discussion will focus on these major delivery barriers and corresponding optimization strategies [8-10].

3. Barriers to in Vivo Delivery of Polymer-Based Nanomedicines and Challenges in Clinical Translation

3.1 Circulatory Phase: Immune Clearance and Structural Stability Barriers

Once nanocarriers enter the bloodstream, they are first exposed to the risk of nonspecific phagocytosis mediated by the reticuloendothelial system and enzymatic degradation in the blood. Unmodified carriers are easily recognized and cleared by macrophages, making it difficult to maintain an adequate circulation half-life. Although polyethylene glycol (PEG) modification can effectively prolong the carrier's retention time in the bloodstream, it may induce the production of anti-PEG antibodies in the body, thereby accelerating the clearance of the carrier following repeated dosing. Furthermore, proteases in the blood can degrade peptide and protein-based targeting ligands, while the protein corona formed by the nonspecific adsorption of blood proteins onto the carrier surface can mask ligand recognition sites, thereby directly impairing subsequent target-recognition efficiency [11].

3.2 Tumor Accumulation and Tissue Penetration: Heterogeneity of the EPR Effect and Matrix Barriers

The enhanced permeability and retention (EPR) effect in solid tumors is the core mechanism by which nanocarriers accumulate in tumor regions. However, this effect exhibits significant heterogeneity: vascular permeability varies markedly across different tumor types, different patients, and even different regions within the same tumor, resulting in limited overall accumulation of most nanocarriers in tumor tissue. Furthermore, the dense extracellular matrix of tumors and elevated interstitial fluid pressure hinder the diffusion of nanocarriers within the tumor parenchyma. Even when carriers reach the vicinity of tumor blood vessels, they struggle to penetrate into deeper tumor regions and reach the vicinity of tumor cells, thereby limiting subsequent cell-targeting processes [12-14].

3.3 Barriers to Cell Recognition, Targeted Uptake, and Intracellular Processing

Once nanocarriers reach the vicinity of tumor cells, they first encounter the problem of cell recognition and targeted uptake. The expression of targeted receptors on the surface of tumor cells is not uniform, and the content of receptors between the primary and metastatic lesions, or even different cell subsets within the same tumor will be greatly different, which makes the recognition effect of targeting ligands uneven, and it is difficult for some tumor cells to complete the endocytosis of nanoparticles. Furthermore, even when a carrier is internalized by a cell and enters an intracellular vesicle, this does not necessarily mean that the active drug has reached its intracellular target. After endocytosis, nanocarriers typically enter endosomes and lysosomes: if the carrier scaffold degrades prematurely, the loaded drug is prone to being broken down by enzymes within the lysosomes. Conversely, if the carrier's drug-release capacity is insufficient, the drug becomes trapped within the vesicles and is difficult to release into the cytoplasm. For nucleic acid-based drugs, difficulty in escaping the vesicles is the primary factor limiting therapeutic efficacy. P-glycoprotein (P-gp)-mediated drug efflux is another intracellular regulatory mechanism that primarily acts on small-molecule substrates and does not significantly affect all nanocarriers and their payloads. Even if the nanocarrier successfully delivers the small molecule drug into the cells, P-gp can still pump the free drug out of the cells, reducing the intracellular effective drug level and weakening the killing effect on tumor cells. It should be noted that this process does not directly interfere with the uptake of the nanocarriers themselves by cells [15-16].

3.4 Clinical Translation: Process Standardization and Long-Term Safety Bottlenecks

In order to achieve composite functions such as targeted stimulus response and multi-drug co-loading, polymer nanocarriers usually require multi-step chemical synthesis and multi-layer surface modification, and the preparation route is lengthy and complex. The complex synthesis and modification processes can lead to

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poor reproducibility between batches, and it is difficult to directly scale up the laboratory-scale preparation process to industrial production. In addition, most studies at present focus on short-term antitumor effects, while long-term biosafety data such as the risk of long-term in vivo accumulation of carriers and potential toxicity of degradation products are still lacking. There is no unified and standardized in vivo and in vitro evaluation standard in the field, and it is difficult to objectively compare and evaluate the targeting efficacy of different carriers, which restricts the translation of nanomedicine from laboratory research to clinical practice [17-18].

4. Optimization Strategies for Polymeric Nanocarriers at Different Stages of Drug Delivery

4.1 Optimization of Blood Circulation: Enhancing Carrier Stability in the Bloodstream Through Biomimetic Camouflage

To address obstacles such as immune clearance and ligand inactivation during the circulatory stage, biomimetic interface engineering strategies are prioritized to enhance carrier stability. Biomembranes, such as those from tumor cells or platelets, are coated onto the surface of polymeric nanocarriers, or exosome-polymer composite carriers are constructed. These biomembrane shells camouflage the carriers to reduce nonspecific adsorption by blood proteins, evade phagocytosis by the reticuloendothelial system, and prevent direct exposure of ligands to the enzymatic environment of the bloodstream. Preclinical studies on cell membrane-coated PLGA nanoparticles have fully demonstrated the application potential of biomimetic interface modification: Red blood cell membrane-coated PLGA achieves immune evasion via the CD47 protein, resulting in an elimination half-life of 39.6 h—significantly longer than the 15.8 h observed for PEG-modified PLGA—with 16% of the administered dose still present in the blood 48 h after administration. PLGA coated with umbilical cord mesenchymal stem cell membranes can reduce nonspecific phagocytosis by macrophages and optimize the in vivo distribution of the carrier. Although practical challenges—such as a complete membrane-coating rate of only 6.2 ± 0.3% with the extrusion method, high raw material consumption, and interference from the protein corona—remain to be addressed, with continued iteration and optimization of membrane preparation and coating processes, this class of biomimetic carriers is expected to further pave the way for translation from the laboratory to clinical treatment [19-20].

4.2 Optimization of Tumor Enrichment and Tissue Penetration: Enhancing Passive Targeting Effects Through Regulation of Physicochemical Parameters

To address the heterogeneity of the EPR effect in solid tumors and the issues of insufficient nanoparticle enrichment and penetration, delivery efficiency can be improved by regulating the type of polymer matrix and the physicochemical parameters of the nanoparticles. Preclinical data indicate that a carrier size range suitable for the tumor EPR effect is 30–200 nm. Particles smaller than 10 nm are easily cleared by the kidneys, while those larger than 200 nm tend to activate the complement system, accelerating immune clearance. In terms of stiffness, stiffer nanoparticles are more readily phagocytosed by macrophages. Softer vesicular carriers are less readily taken up by macrophages, can pass through tissue filtration pores, achieve longer circulation times, and facilitate tumor accumulation. Morphology also influences delivery. Rod-shaped and worm-shaped non-spherical nanocarriers, compared to spherical particles, can achieve longer circulation times and higher extravasation efficiency into tumors. However, this effect is tumor-type dependent and is not a universal rule. Even with optimized physicochemical parameters, existing nanocarriers still have inherent limitations. A meta-analysis shows that 24 hours after intravenous injection of nanomedicines, only 0.76% of the administered dose reaches solid tumor sites, and this figure further drops to 0.35% after 168 hours. The EPR effect differs significantly between human-derived tumors and transplanted tumors in animals. Relying solely on physicochemical modulation to enhance passive targeting makes it difficult to achieve ideal tumor enrichment and deep penetration. Precise fine-tuning of various physicochemical properties is a crucial foundation for carrier design. When combined with active targeting and intracellular stimulus-responsive drug release strategies, this approach is expected to gradually overcome EPR-related delivery limitations and advance the development of nanomedicine delivery systems toward clinical application [21-23].

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4.3 Optimization of Cellular Uptake: Active Targeting Modification Mediated by Stable Ligands

Active targeting modification strategies are optimized to address insufficient target-recognition specificity caused by tumor heterogeneity and the risk of single-target escape. The screening of ligand types, surface modification methods, and control of grafting density are key to reducing the risks of enzymatic inactivation and protein corona masking, as well as improving targeted recognition efficiency. Small-molecule ligands (such as folic acid and galactose), peptides, and antibody-based ligands each have their own advantages and disadvantages, and should be selected appropriately based on the specific application scenario. Numerous preclinical studies on related polymeric vesicles have also fully demonstrated the regulatory value of ligand type selection and targeting group modification on active targeting efficacy. PSMA-targeting peptide 563-modified P (OEGMA)-PDPA polymeric vesicles selectively deliver the BikDDA gene to LNCaP prostate cancer cells by actively recognizing PSMA receptors on the surface of prostate cancer cells. In contrast, polymeric vesicles composed of the same components but without grafted targeting ligands did not exhibit this cell-selective uptake, clearly demonstrating that active targeting modifications confer tumor-recognition capabilities to the carrier. Angiopep-2-modified PCL-PEOz polymeric vesicles achieve active targeting through the specific binding of the ligand to the LRP1 receptor. Studies confirmed that a 20% Angiopep-2 grafting density is the optimal active-targeting parameter for achieving blood-brain barrier (BBB) penetration. In an orthotopic mouse model of glioblastoma, these active-targeting polymeric vesicles demonstrated significantly enhanced BBB penetration and greater accumulation at the glioma lesion site compared to non-targeted polymeric carriers. PEG-P(TMC-DTC) polymeric vesicles modified for CD44 targeting act on MDA-MB-231 triple-negative breast cancer cells via receptor-mediated endocytosis. Compared to polymeric vesicles of the same system without targeting-group modification, the targeted group exhibited higher binding and uptake efficiency in tumor cells, and antitumor activity was significantly improved. Although protein corona masking and tumor receptor heterogeneity may interfere with targeted recognition, through rational screening of ligand types and precise regulation of ligand grafting density, there remains considerable room for optimization of the active targeting performance of polymeric carriers, providing a feasible modification strategy for achieving efficient and selective uptake by tumor cells [24-25].

4.4 Optimization of Intracellular Release: Design of Synergistic Drug Release in Response to Multiple Tumor Microenvironmental Stimuli

To address premature drug leakage, insufficient intracellular release, and multidrug resistance, stimuli-responsive structural units—such as pH-sensitive, reduction-sensitive, enzyme-sensitive, and hypoxia-sensitive units—can be incorporated into polymer chains to construct carriers with single-stimulus responsiveness or synergistic responsiveness to multiple stimuli. The structure of the carrier was stable under the normal physiological environment of blood circulation, and the drug was encapsulated in the carrier. When it reaches the tumor microenvironment or enters the inside of tumor cells, external stimuli trigger the macromolecular chain segment breakage or conformational change, and the carrier disassembles and releases the drug, so as to realize the targeted enrichment of the carrier and site-specific drug release at the lesion, reduce the drug exposure in normal tissues, and reduce the off-target toxicity. This strategy has been preclinical validated in the nanogel system. The disulfide-modified, reduction-responsive nanogel exploited the glutathione (GSH) concentration gradient between the cytosol (2–10 mM) and the extracellular space (2–20 μM). Following cellular uptake, cleavage of the disulfide bonds enabled doxorubicin release in MCF-7 breast cancer cells. The pH-responsive NIPAAm/ chitosan nanogel inhibited drug leakage at pH 7.4 and accelerated the release of camptothecin and paclitaxel in the acidic environment of the tumor at pH 6.8. Animal model experiments showed that the system could induce complete tumor regression in more than half of tumor-bearing mice. The enzyme /pH dual-responsive branched nanogel can degrade in response to the combined signals of intracellular acidity and high enzyme expression, and complete the intracellular drug release in MDA-MB-231 cells, reducing the risk of premature drug leakage caused by the failure of a single stimulus response. Tumor heterogeneity leads to significant fluctuations in pH value, GSH level and enzyme expression level between different lesions, which leads to unstable drug release efficiency. At the same time, there are differences between tumor microenvironment signals and intracellular signals, and it is difficult to take into account the drug release at the tumor stroma level by only using intracellular stimulation to trigger drug release.

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Future carrier design needs to take into account in situ responses to the tumor microenvironment and intracellularly triggered drug release to further improve the controllability of drug release at the lesion site [26].

4.5 Optimization of the Clinical Translation Process: Simplification and Standardization of Polymer Preparation Processes and Establishment of an Evaluation System

To overcome translation barriers such as complex synthesis steps, poor batch-to-batch stability, and a lack of evaluation standards, both delivery performance and formulation manufacturability should be considered simultaneously during the carrier design phase. By simplifying polymer synthesis, surface modification, and nanoformulation assembly processes, the lengthy multi-step chemical reactions can be reduced. Optimizing the nanocarrier preparation process will enhance the reproducibility of the manufacturing process. At the quality evaluation level, key quality attributes such as particle size distribution, drug loading capacity, in vitro drug release behavior, and batch consistency must be prioritized. Concurrently, in vitro and in vivo evaluation protocols should be refined to establish methods for assessing targeting performance that more closely mimic the actual in vivo environment. The long-term in vivo safety of polymer carriers and their degradation products should be systematically evaluated, and unified evaluation standards should be established for core quality indicators and biological evaluation to support the clinical translation research of polymer-based nanomedicines [27, 28].

5. Summary and Outlook

Due to their high modifiability and broad drug-loading spectrum, polymeric nanocarriers represent a key technological system in the field of targeted cancer drug delivery. A series of optimization strategies have been developed to address the respective bottlenecks at different stages of the delivery process: biomimetic surface modification can improve the carrier's stability in the bloodstream. Regulation of physicochemical parameters can further enhance tumor accumulation and tissue penetration. Stable ligand modification can improve the efficiency of tumor cell recognition and uptake. And multi-microenvironment-responsive designs can ensure precise intracellular drug release, while research on process standardization provides support for overcoming barriers to clinical translation. However, existing strategies still face inherent limitations that are difficult to overcome: the heterogeneity of the EPR effect determines the upper limit of passive targeting. The complex biological environment in vivo weakens the actual efficacy of active targeting. The high heterogeneity of tumors is also difficult to address fully with a single carrier strategy. And insufficient process scale-up and long-term safety evaluation of multifunctional carriers similarly constrain their clinical translation. Future research and development must strike a balance between targeting efficacy, biosafety, and industrial feasibility; promote carrier designs that integrate multiple strategies; simplify preparation processes; and establish a comprehensive long-term safety evaluation system to gradually overcome biological barriers [29-30].

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