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Research Advances in Micro/Nanomotors for Tumor Therapy

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Abstract: *Micro/nanomotors represent a novel class of active drug delivery platforms. By leveraging their autonomous propulsion and microenvironment-responsive characteristics, these platforms exhibit great potential in addressing key challenges of conventional cancer therapies, such as poor targeting specificity, susceptibility to drug resistance, and difficulties in overcoming biological barriers within tumors. This review begins with an overview of the propulsion mechanisms of micro/nanomotors, including chemical, physical, and biological approaches. Subsequently, it provides a systematic discussion on the recent research progress in three pivotal areas: targeted drug delivery, regulation of the tumor mechanical microenvironment, and diagnostic-therapeutic integration. Despite existing challenges related to biosafety, in vivo navigation accuracy, and clinical translation, interdisciplinary convergence and continuous design optimization are anticipated to facilitate the substantive application of intelligent micro/nanomotors in precise tumor therapy in the future.*

Keywords: *Micro/Nanomotors, Tumor, Therapy*

1. Introduction

Recent data indicate that approximately 20 million new cancer cases and 10 million cancer deaths are reported globally each year[1,2]. Cancer has become a major clinical and public health challenge worldwide. Conventional treatment modalities, including surgery, radiotherapy, and chemotherapy, often cause significant toxicity to normal cells due to their poor targeting specificity. Furthermore, these therapies can induce multidrug resistance in tumor cells during treatment, thereby substantially compromising their therapeutic efficacy[3]. The tumor microenvironment is a complex system composed of tumor cells and their surrounding components, such as immune cells, inflammatory cells, cancer-associated fibroblasts, adjacent stromal tissue, microvessels, as well as various cytokines and chemokines[4-6] . This environment is typically characterized by three hallmarks: hypoxia, chronic inflammation, and immune suppression, all of which pose significant barriers to effective cancer treatment. Additionally, the dense extracellular matrix forms a formidable physiological barrier within tumors, which severely restricts the penetration of therapeutic nanomedicines into solid tumors and the infiltration of immune cells[7,8]. Consequently, modulating the tumor microenvironment and overcoming its associated physiological barriers are considered key strategies for enhancing the efficiency of cancer therapy.

Distinct from conventional nanomaterials, micro/nanomotors present a novel strategy for tumor therapy due to their favorable biocompatibility. Their unique size advantages and superior motile capabilities endow them with significant potential in targeted delivery, controlled drug release, imaging diagnosis, and tumor therapy. To overcome the constraints imposed by low-Reynolds-number fluid environments and Brownian motion, micro/nanomotors can utilize diverse propulsion mechanisms powered by chemical energy, physical fields, or biological molecules. This active propulsion mode enables them to effectively traverse physiological barriers such as dense extracellular matrix, the blood-brain barrier, and the blood-tumor barrier, moving beyond reliance on passive diffusion or circulatory transport alone[9,10].Consequently, micro/nanomotors hold broad prospects for enhancing tumor-targeting precision and achieving deep-tissue penetration.

The unique autonomous propulsion capability of micro/nanomotors offers innovative solutions to key challenges in cancer research. This capability not only promotes the development of multimodal propulsion strategies but also accelerates their application in integrated tumor diagnosis and therapy.

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Although micro/nanomotors demonstrate significant advantages in cancer treatment, their clinical translation faces multiple challenges, primarily concerning biocompatibility, long-term in vivo safety, and precise targeting and navigation. To address these challenges, researchers are actively exploring diverse propulsion mechanisms and advanced surface functionalization strategies. These efforts aim to comprehensively enhance the overall performance and biological applicability of micro/nanomotors. This review systematically outlines the primary propulsion mechanisms of micro/nanomotors and their functional applications in cancer diagnosis and therapy. Building upon this foundation, the article further analyzes and prospects the clinical translation potential and future development trends of this technology considering current research progress.

2. Propulsion Mechanisms of Micro/Nanomotors

Unlike traditional colloidal particles or nanocarriers that rely on Brownian motion for passive diffusion, artificial micro/nanomotors utilize their autonomous propulsion and navigation capabilities. This approach holds promise for overcoming the limitations of current delivery systems and achieving active targeted drug delivery. Based on their propulsion mechanisms, micro/nanomotors can be primarily categorized into three types: physically powered, chemically powered, and biologically powered.

2.1 Chemically Powered Micro/Nanomotors

Chemically powered micro/nanomotors can harness specific chemical substances within the tumor microenvironment to generate propulsion through catalytic or spontaneous reactions. Such systems typically require the integration of catalysts or reactants within or on the surface of the nanostructure, relying on corresponding substrates as fuel. In current research, the selection of chemical fuels is often guided by the characteristic features of the tumor microenvironment. Among these, hydrogen peroxide (H_2O_2) is one of the most extensively utilized chemical fuels. For instance, Tan et al. constructed a soft nanomotor for delivering the photosensitizer Ce6, based on soft mesoporous organosilica and catalase[11]. This nanomotor employs catalase to catalytically decompose H_2O_2 present in the tumor microenvironment, thereby generating oxygen. This reaction not only provides propulsion for the nanomotor, enhancing its tumor penetration and cellular internalization, but also improves the efficacy of photodynamic therapy through oxygen supply and demonstrates a potential inhibitory effect on lung metastasis. In another study, Shi et al. constructed a hyaluronic acid-coated, inorganic catalase-driven Janus nanomotor[12]. This system efficiently decomposes H_2O_2, effectively alleviates the burden of bacterial infection, and simultaneously demonstrates favorable drug-loading capacity. In addition, current research is also focusing on utilizing specific endogenous substances that are highly expressed in the tumor microenvironment, such as lactate and glutathione (GSH). This approach aims to achieve targeted movement of micro/nanomotors at the tumor site while simultaneously modulating the tumor microenvironment. Fan et al. developed a class of intelligent nanorobots[13]. Their design integrates palladium nanozymes possessing catalase/peroxidase activity with lactobacillus-derived outer membrane vesicles loaded with lactate oxidase and D-lactate dehydrogenase. The palladium nanozymes provide propulsion, while the vesicles are responsible for targeted delivery and metabolic reprogramming of tumors. This system utilizes endogenous H_2O_2 to catalytically generate O_2 for propulsion. Subsequently, it synergistically achieves metabolic-immune reprogramming and chemodynamic therapy in solid tumors. Liu et al. constructed an asymmetric feather-sphere magnetic nanorobot platform featuring a microporous tail structure[14]. This platform electrostatically adsorbs and loads lactate dehydrogenase, catalase, and triptolide. It not only catalyzes the conversion of H_2O_2 to O_2 for self-propulsion but also simultaneously degrades lactate, thereby effectively alleviating the hypoxic tumor microenvironment. Separately, Yu et al. constructed a glucose-fueled enzymatic nanomotor by encapsulating glucose oxidase, catalase, and chlorin e6 within a cisplatin-based zeolitic imidazolate framework[15]. This nanomotor utilizes a cascade enzymatic reaction to generate O_2 for propulsion while concurrently depleting the overexpressed glutathione within tumors. Consequently, it significantly enhances the efficacy of synergistic therapy.

To expand their applications in the biomedical field, various propulsion mechanisms reliant on distinct gaseous byproducts have been developed to accommodate diverse therapeutic contexts. Among these, micro/nanomotors propelled by the catalytic decomposition of urea to generate CO_2 and NH_3 have garnered considerable attention for bladder cancer therapy. For instance, Simó et al. demonstrated radiolabeled mesoporous silica-based urease-powered nanorobots in an orthotopic bladder cancer mouse model[16]. This system utilizes urease to catalyze the urea reaction, generating gas bubbles for propulsion. This process significantly enhances the accumulation, penetration, and retention of the nanorobots within tumors, underscoring their potential as efficient delivery vehicles for bladder cancer treatment. Beyond

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urea-driven systems, other gas-propelled strategies have also been employed to potentiate tumor therapy. Zhao et al. developed an X-ray-activatable nanomotor with a core composed of an iron carbonyl prodrug framework encapsulating the TLR7 agonist R848[17]. Upon X-ray irradiation, the FeCO framework rapidly decomposes, producing carbon monoxide bubbles. These bubbles propel the nanomotor for deep penetration and prolonged retention within colorectal tumor tissues while concurrently enhancing DNA damage. The sequential release of R848 further triggers a robust immune response. Separately, Ma et al. designed a nitric oxide-driven hollow gold Janus nanomotor[18]. The generated NO not only propels the nanomotor for tumor penetration but also promotes intratumoral T cell infiltration, thereby enhancing the efficacy of immunotherapy. In summary, while chemically powered micro/nanomotors demonstrate significant advantages, achieving stronger propulsion performance and meeting stringent biomedical requirements in the future will necessitate more flexible and systematic optimization of their structural design and surface functionalization.

2.2 Physically Powered Micro/Nanomotors

Compared to chemically powered systems, physically powered artificial micro/nanomotors achieve sustained locomotion and remote directional control through the application of external stimuli, such as light, heat, acoustic waves, electricity, or magnetic fields. This approach typically avoids inducing systemic toxicity. Among these modalities, magnetic field-driven and light-driven systems have attracted significant attention in the field of tumor therapy due to their favorable biocompatibility and high controllability.

Light-driven micro/nanomotors convert optical energy into mechanical motion, relying on a propulsive force generated by an asymmetric field in their surrounding medium. The inherent properties of light, such as wireless remote transmission, precisely tunable energy, and reversible on/off switching, enable these motors to achieve non-invasive therapy with high spatiotemporal precision. For example, Venturi et al. designed a biodegradable Au-gas vesicle nanomotor[19]. Under laser irradiation, it achieves high-speed propulsion by generating a localized temperature gradient, thereby enhancing tissue penetration and improving the efficiency of intracellular drug delivery and accumulation at the target site. It should be noted that this study has so far only been validated at the cellular level, and further animal experiments are required for confirmation. Furthermore, light-driven micro/nanomotors can often be combined with phototherapeutic strategies to enhance anti-tumor efficacy. Song et al. constructed a multifunctional copper silicate-based nanomotor ($CuSiO_3$@Au-Pd NMs) by integrating Au-Pd nanoalloys with flower-like copper silicate[20]. Upon near-infrared laser irradiation, this nanoparticle utilizes the photothermal effect to create a local thermal gradient. This mechanism not only enables light-driven enhanced tumor penetration but also synergizes with photothermal therapy, demonstrating promising anti-tumor activity. Currently, research on light-driven micro/nanomotors predominantly focuses on the near-infrared wavelength range. Future work could be extended to ultraviolet or even natural light-driven systems to broaden their application scenarios and enhance clinical translation potential.

Magnetic fields not only provide propulsive force for micro/nanomotors but also enable precise spatial navigation, making them an ideal power source for physically powered micro/nanosystems. In early research, Dasgupta et al. constructed a helical nanostructure containing ferromagnetic elements and applied it to probe the local three-dimensional tissue culture microenvironment[21]. This system demonstrated promising potential for applications in cancer diagnosis and imaging, quantitative analysis of tumor invasiveness, and in vivo drug delivery. The physical characteristics of micro/nanomotors, such as size and shape, significantly influence their penetration ability within tumor tissues. Zhu et al. developed a deformable nanocarrier (DAT-PPED&F) that can undergo shape transformation under magnetic actuation[22]. The application of an external magnetic field substantially enhances the deep-tissue penetration capability of this flexible nanoparticle. Additionally, the acidic environment within tumor tissue can further activate the cell-penetrating peptide TAT, thereby further improving the tumor penetration efficiency of the nanoparticle. Furthermore, magnetic navigation can be integrated with optical therapy to achieve precise tumor intervention. Guo et al. constructed a microrobot based on photosensitizers doped with magnetic nanoparticles and Nile Red[23]. This microrobot can be magnetically guided to target tumor regions. Subsequently, excitation by a 530 nm pump laser induces the generation of 650 nm coherent laser emission, which precisely activates the photosensitizer to achieve localized tumor cell ablation.

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2.3 Biologically Powered Micro/Nanomotors

In contrast to physically and chemically powered micro/nanomotors, which often rely on external equipment and are constrained by limited energy penetration depth, biologically powered micro/nanomotors leverage intrinsic taxis or biomimetic propulsion mechanisms. This characteristic endows them with unique application potential and has attracted extensive research interest in recent years.

Utilizing motile bacteria as driving engines represents a major research direction in biologically powered micro/nanomotors. Certain anaerobic bacteria are frequently employed as bio-hybrid delivery vehicles due to their inherent tropism toward hypoxic regions within tumors. For instance, Huang et al. anchored liposomes onto the surface of engineered Salmonella, constructing micro/nanomotors capable of autonomous navigation to tumor sites with deep penetration[24]. This system can establish a closed-loop immune response activation within the tumor microenvironment, offering a customizable delivery platform for cancer immunotherapy. In another study, Zhu et al. proposed the concept of an “AIEgen-bacteria hybrid bionic robot”[25]. This design integrates the hypoxic-targeting property of Escherichia coli Nissle 1917 (EcN) with the optical functions of aggregation-induced emission luminogens, thereby achieving integrated multimodal imaging and therapy of tumors.

Furthermore, micro/nanomotors based on endogenous cells, such as neutrophils, macrophages, and platelets, also demonstrate significant advantages in targeted tumor therapy. These systems leverage the innate tropism and excellent biocompatibility of the cells to achieve precise drug delivery while reducing the risk of immune clearance. For example, Gao et al. developed a “Trojan robot” system by loading enzymatic nanorobots into neutrophils[26]. This system utilizes inflammatory gradients to drive neutrophils across the blood-brain barrier, thereby targeting glioblastoma. Upon reaching the tumor microenvironment, inflammatory signals trigger the release of the nanorobots. Subsequently, the nanorobots harness locally present H_2O_2 for catalytic propulsion, enabling further localization at the disease site. In another approach, Geng et al. constructed engineered platelet-based nanocarriers[27]. This system specifically targets both primary and metastatic tumors, enhancing the safety and efficacy of drug delivery and offering a novel strategy for hierarchical targeting therapy. Looking forward, to further expand the therapeutic potential of biologically powered micro/nanomotors, future research could focus on exploring designs utilizing other living systems and biomimetic structures, thereby promoting their application in clinical precision medicine.

3. Application Advances of Micro/Nanomotors in Tumor Therapy

3.1 Targeted Drug Delivery

Traditional drug delivery systems primarily rely on the enhanced permeability and retention (EPR) effect, yet they exhibit limited targeting specificity and significant heterogeneity. These systems struggle to achieve deep tumor penetration, resulting in an extremely low drug accumulation rate within tumor tissue, non-uniform therapeutic efficacy, and pronounced systemic toxicity[28,29]. To address these challenges, micro/nanomotors offer a novel delivery strategy capable of spatiotemporally precise regulation, leveraging their autonomous propulsion and microenvironment-responsive drug release characteristics.

In the treatment of bladder cancer, traditional nanomedicines face challenges in intravesical instillation therapy. The glycosaminoglycan layer of the bladder wall impedes drug penetration, and frequent urination leads to rapid drug clearance, creating an urgent need for novel systems capable of efficient and rapid delivery to the bladder wall. Self-propelled micro/nanomotors demonstrate considerable potential due to their advantages in directional chemotactic motion, robust penetration of biological barriers, and rapid drug transport. For instance, Chen et al. developed a light-driven hydrogel nanomotor[30]. Under the synergistic regulation of a magnetic field and near-infrared light, its autonomous motion significantly enhanced the efficacy of chemodynamic therapy in a bladder perfusion model. Separately, Choi et al. constructed a urease-powered nanomotor loaded with a STING agonist, based on chitosan and heparin[31]. This system harnesses urea present in urine to achieve ballistic motion and swarm behavior, thereby enabling efficient delivery of immunotherapeutic agents and advancing immunotherapy for bladder cancer. In colorectal cancer treatment, the mucus layer and epithelial cell barriers severely restrict drug delivery efficiency. To address this, Wang et al. developed a biomimetic dual-driven nanomotor with a propulsion unit composed of mesoporous silica nanoparticles and polydopamine[32]. Under infrared light irradiation, this nanoparticle generates self-propulsion through the

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photothermal effect while also asymmetrically producing nitrogen gas to provide gas thrust. This approach enables the nanomotor to overcome multiple intestinal barriers, increasing cisplatin delivery efficiency by 3.5-fold and achieving a 98.6% tumor suppression rate in animal models. Looking ahead, with a deeper understanding of disease microenvironments and biological barrier mechanisms, the design of micro/nanomotors is expected to become more targeted and intelligent. This progress holds promise for enabling more precise and efficient therapeutic applications in clinical translation.

3.2 Mechanical Disruption

The tumor mechanical microenvironment constitutes a complex system comprised of tumor cells, fibroblasts, immune cells, and non-cellular components. Mechanical signals within this system play a crucial regulatory role in tumor biological behavior. Aberrant mechanical properties, a hallmark of solid tumors, not only provide a physical barrier for tumor cells to evade immune surveillance but also play a pivotal role in tumor progression, recurrence, and metastasis. Consequently, remodeling the mechanical microenvironment to overcome physical barriers and enhance therapeutic efficacy has emerged as a novel research direction in solid tumor therapy. For example, Fan et al. proposed an intracellular magneto-mechanical regulation strategy that combines actin-targeted magnetic nanomotors with a rotating magnetic field[33]. Under a low-frequency magnetic field, these nanomotors assemble into rod-like structures, acting as magneto-mechanical transducers to efficiently generate mechanical forces on the actin cytoskeleton. This enables localized remodeling of the tumor mechanical microenvironment within cells, offering a novel approach for in vivo intervention. In recent years, researchers have focused on developing micro/nanomotors capable of actively applying disruptive mechanical forces to overcome material limitations and circumvent traditional therapeutic resistance. Zhang et al. reported an organic Janus-type nanomotor[34]. Upon light irradiation, it asymmetrically generates reactive oxygen species and surface thermal gradients, driving thermophoresis and autonomous propulsion. This process subsequently applies targeted nanomechanical forces and modulates mechanotransduction pathways, successfully inducing cancer cell pyroptosis and activating anti-tumor immunity. Furthermore, Tao et al. constructed atom-edged magnetic nanomotors based on graphene oxide and cubic magnetic nanoparticles[35]. Regulated by a three-dimensional rotating-fluctuating magnetic field, these motors execute a unique "rotate-and-bounce" motion trajectory. This amplifies the local pressure on lysosomal membranes by 8.1 to 37.5-fold, thereby efficiently triggering lysosomal membrane perforation and killing tumor cells. This approach overcomes the localization limitation of mechanical forces inherent to conventional magnetic motors. Collectively, studies directly intervening in cellular structure and function via nanomechanical forces provide a novel physical approach to tumor therapy with promising application prospects.

3.3 Diagnostic-Therapeutic Integration

Micro/nanomotors demonstrate unique advantages for diagnostic-therapeutic integration. They not only actively navigate to target tissues, significantly enhancing the local concentration of contrast agents and thereby improving imaging signals, but also overcome biological barriers to achieve tissue penetration depths exceeding 100 micrometers[36]. Furthermore, micro/nanomotors can be co-loaded with imaging probes and therapeutic agents, enabling simultaneous imaging and treatment. Magnetic resonance imaging, known for its high soft-tissue resolution and deep penetration, holds significant advantages in image-guided therapy. For instance, Sun et al. constructed a theranostic nanomotor (FeO@mSiO$_2$/Au-CAT) based on magnetic nanoparticles[37]. In this system, the superparamagnetic FeO@mSiO$_2$ nanoparticles serve for T_2-weighted MRI and chemodynamic therapy; the Au shell forms the Janus structure for photothermal therapy; while the catalase on the opposite side activates nanomotor motion via self-diffusiophoresis and catalyzes the production of O_2 to alleviate tumor hypoxia. In another study, Zhang et al. developed a Janus-type hollow MnO_2 nanomotor[38]. Within the tumor microenvironment, it decomposes into Mn^{2+} to enhance MRI signals while simultaneously catalyzing H_2O_2 to generate O_2, which both alleviates hypoxia and provides propulsion for the nanomotor. These findings indicate that Janus-type MRI nanomotors offer a novel strategy with clinical translation potential for multimodal therapy in cancers such as pancreatic cancer. Ultrasound imaging, as a non-invasive, safe, cost-effective technique with great penetration depth, has also garnered attention in theranostics. Chen et al. designed a novel Janus-structured mesoporous organoplatinum nanomotor[39]. The encapsulated perfluorohexane undergoes a liquid-to-gas phase transition upon laser excitation, generating microbubbles that both propel the nanomotor into tumor tissue and enhance acoustic signals in the tumor region. This enables visual tumor localization and treatment monitoring, thereby advancing ultrasound imaging-guided glutamine metabolism inhibition-photothermal synergistic therapy. Photoacoustic imaging combines the high contrast of optical imaging with the deep penetration of ultrasound, providing high-resolution, real-time, and precise tumor localization. Xu et al. constructed a dual-triggered nitric oxide nanomotor[40]. Its pellet-like asymmetric structure simultaneously generates a temperature gradient and releases nitric oxide under near-infrared light excitation, driving nanomotor propulsion. Leveraging the incorporated photoacoustic imaging contrast agents, this system can identify optimal treatment areas and intervention timing to enhance therapeutic efficacy. Looking forward, with the further integration of multimodal imaging and intelligent propulsion technologies, theranostic micro/nanomotors are expected to play an increasingly important role in precision cancer medicine, offering new breakthroughs for clinical therapy.

4. Conclusion

The development of micro/nanomotors has opened broad prospects for intelligent tumor diagnosis and therapy. Currently, a series of breakthrough advancements in this field have convincingly demonstrated the significant application value of micro/nanomotors in tumor nanomedicine. This review has systematically outlined the primary propulsion mechanisms of micro/nanomotors and summarized their latest research progress in three key areas: targeted drug delivery to tumors, mechanical intervention in the tumor microenvironment, and diagnostic-therapeutic integration.

Despite the considerable potential demonstrated by micro/nanomotors in cancer therapy, their clinical translation still faces multiple challenges. Firstly, the sensitivity and specificity of their chemotactic navigation require improvement to effectively cope with the interference from the complex biochemical environment in vivo. Secondly, a systematic biosafety evaluation framework is yet to be established. Current research predominantly focuses on in vitro and short-term in vivo experiments. However, critical safety concerns regarding long-term in vivo immune responses, organ accumulation toxicity, metabolic pathways, and potential micro-mechanical damage induced by autonomous motion necessitate further in-depth investigation and the establishment of standardized evaluation protocols.

Despite the challenges related to material biocompatibility, multifunctional integration, and clinical translation pathways, continuous interdisciplinary convergence and technological iteration are expected to drive the development of smarter and safer micro/nanomotor systems. This progress holds the promise of ultimately facilitating their substantive clinical application in the field of precise tumor therapy.

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