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Research on the application of micro-robotics in the drug delivery field

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Abstract. Drug delivery has been one of the hotspots of research in the field of pharmacy. Delivering drugs to the target location more accurately and efficiently is a problem that researchers have been thinking of facing. The invention of the microrobot has led to greater convenience in the field of micromanipulation. Microrobots have demonstrated exceptional promise and significant benefits in the field of medication delivery in recent years, owing to their versatility, low invasiveness, and controllability. This paper comprehensively reviews the research on microrobots for drug delivery applications. First, we summarize the microrobot's in vivo motion technology from the propulsion mode perspective and discuss its effects. Subsequently, we analyze the new technologies in the field related to microrobots used for drug-targeting applications and explore the release method of the drug to reach the target location. Finally, synthesizing the analysis results, we give the problems and future development of microrobot applications in the field of drug delivery.

Keywords: microrobots, drug delivery, drug release, braking technology for microrobots

1. Introduction

How to realize more accurate and efficient drug delivery has been one of the hotspots in pharmacy. In recent years, microrobots have been more frequently used in drug delivery, showing unique potential and great advantages [1].

In this paper, we comprehensively review the research on microrobots for drug delivery applications. First, the topic of in vivo microrobot locomotion techniques is examined from the standpoint of various propulsion systems, including biochemical reactions and motile microorganisms for self-propulsion and electromagnetic, optical, and acoustic fields for external field propulsion. The benefits and main drawbacks of each system are also examined. Subsequently, recent advances in the field of micro-robot-driven targeted drug delivery are reviewed, along with the relevant drug release processes and the potential applications of new 4D technology. Although most of the current studies on microrobots in the field of drug delivery have been conducted in vitro, cases of their application to living organisms have gradually increased in recent years. Finally, we summarize and discuss the challenges and future trends of microrobot technology in drug delivery.

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Here, we use the research method of case study and comparative analysis to synthesize the cases of microrobot discovery and development in recent years to analyze the novel applications of microrobots in the field of drug delivery and help the further development of micromachines in drug targeting.

2. In vivo braking technology for microrobots

A microrobot can reach confined areas inaccessible to traditional robots and perform high-resolution precision operations. However, due to its size constraints, it cannot load an integrated power supply like other intelligent machines. Therefore, there is a need to find new strategies for driving microrobots.

2.1. Self-propulsion microrobots

2.1.1. Biological or chemical reaction driven. Microrobots that use chemical reactions as a driving force were invented earlier and rely on converting chemical energy into mechanical energy for driving by loading chemical fuels on the microrobot.

Chemically driven microrobots provide limited biomedical uses due to the hazardous nature of chemical fuels. There has been quite a bit of attention lately on creating microrobots that run on biocompatible fuels. The primary component of this type of robotic propulsion is self-propelled particles, which break the microrobot by producing internal power through chemical or biological processes like thermophoresis, diffusion electrophoresis, etc [2]. So far, researchers have used two main approaches, i.e., employing enzymes as catalysts to power microrobots [3], or creating microrobots that run on biocompatible fuels like glucose [4], and citric acid [5].

2.1.2. Motile microorganisms driven. Traditional microrobots are gradually being replaced as research progresses. People are beginning to make more machines that combine motile microorganisms with microrobots. Living organisms in nature have evolved biomaterials with rich functions, and hybrid robots combining the characteristics of living organisms with mechanical functions are attracting more and more attention.

Microalgae are very useful as vectors due to their ease of cultivation, fast and efficient propulsion (>100μm/s), autofluorescence, and light-ward guidance. They are also minimally invasive and can reach deeper regions of the body. A majority of them permit surface changes for drug loading on the cell wall, have low cytotoxicity, and are biocompatible with healthy mammalian intercellular structures. In recent years, different morphologies of algae, including spirals, ellipsoids, and spheres, have been used to create microrobots.

Bacteria, as carriers of microrobots, can utilize biochemical energy to move flagella exhibiting strong motility. Advancing in a microscale environment, bacteria have more sensitive chemosensory capabilities that enable drug delivery across different physio-pathological gradients. Researchers have genetically engineered bacteria to reduce cytotoxicity and increase the expression of targeted surface molecules, making them more suitable for targeted delivery in vivo.

Cells (e.g., erythrocytes, spermatocytes, leukocytes, and several other cells) have excellent escape mechanisms and biocompatibility, and these properties can be transferred to micro- and nanorobotic systems to aid in drug delivery. A substantial portion of their membrane systems' immunosuppressive qualities shield the payload from phagocytosis and enable quick renal filtration clearance, lowering medication toxicity in healthy tissues. Sperm cells are likewise flagellated and exhibit a powerful motile phenotype, which according to available studies, has a strong attraction to targeting cancerous lesions of the female reproductive organs. In addition, leukocytes such as neutrophils function as immune cells with autonomous targeting of pathogens for effective drug delivery [2,6].

3. External-field propulsion microrobots

However, microrobots driven by biochemical reactions are mostly toxic due to the fuel. Microrobots carried by microorganisms, such as bacteria, cells, algae, etc., have their own physiological traits and distinct motions that make them difficult to move along a predetermined path and prone to chaotic

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motions. Therefore, there is still a need for external forces to stimulate the actuator, which can provide very precise localization and control of the microrobot, while also compensating for the lack of its power [7].

3.1.1. Magnetic drives. Magnetic actuated systems can utilize magnetic fields for highly accurate delivery in complex blooming biofluids and, at the same time, can be used in opaque and confined environments and at large penetration depths. They exhibit relatively reliable maneuverability and higher degrees of freedom, providing more significant advantages in terms of precision and control. In addition, magnetic fields are biocompatible power sources that can penetrate biological materials without destroying them, causing less harm to the life form to be delivered.

The magnetic gradient force and magnetic moment are the two primary physical effects of the magnetic field that govern this kind of microrobot. Magnetic gradient forces are produced in an inhomogeneous magnetic field when the magnetic microrobot is drawn to regions with a greater magnetic flux density. A magnetic moment is experienced by a magnetic microrobot in a magnetic field, causing it to align with the field. Using the magnetic moment, rotating or oscillating the magnetic field can produce spatial motion of the magnetic microrobot in a fluid medium [1].

However, magnetic field actuation currently suffers from the problem that metals added to core materials or surface coatings will limit their application in vivo.

3.1.2. Optical drives. Optical drives have also received more attention in recent studies. Although microrobots using chemical fuels as an energy source can move quickly, their toxicity still cannot be ignored. So, attention has shifted to optical field drives that can penetrate 1-2 centimeters under the skin. In blood vessels, light-filed drives have the advantage of remote control. At the same time, optical field drives have high instantaneous energy and exhibit high-speed motion. The driving action of optical actuation comes more from the structure of the robot or the asymmetry of the structure of the driving part, providing greater design flexibility. The current limitation problem mainly exists in the fact that the light is not stable and controllable, and it isn't easy to penetrate deep tissues.

There are three main types of light field-driven microrobots currently available. Phototropic organisms, as carriers of microrobots, have a natural phototropism. The use of light-induced temperature gradients as a propulsion mechanism has led to the widespread attention of light-triggered thermophoresis robots that use gels. Photothermal or photocatalytic microrobots drive nanorobots through light-energy-induced and catalytic reactions inside the robot. Optical tweezers-based particle manipulation can achieve higher flexibility in microscale manipulation and has great potential in drug delivery [2].

3.1.3. Acoustic manipulation. Acoustic actuation is a compelling source of remote propulsion for microrobots in microfluidic space. The acoustic field has been made one of the most typical biocompatible power sources. It is so penetrating that it can penetrate the entire human body capable of contactless control while achieving low power and small size. Acoustic field control does not require the introduction of other auxiliary particles and has a high degree of safety. However, the current research on the optimization of acoustics is insufficient, as well as the application of ultrasound may lead to oxidative stress in the cell, and further development is still needed.

Acoustic tweezers can be divided into three categories: standing wave, traveling wave, and acoustic flow. While comparatively easier to use, acoustic flow tweezers are challenging to use in intricate human anatomy. We anticipate realizing drug delivery control of microrobots in the human body with the first two more flexible and maneuverable acoustic tweezers [2,8].

4. Microrobot-driven targeted drug delivery and drug release

The development of microrobots has made great achievements in recent years, as researchers continue to focus on the development of in vivo actuation techniques for microrobots and the reduction of

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biotoxicity. At present, there have been various studies proposing targeted delivery and drug release methods for microrobots. And a few have attempted to operate in vivo.

4.1. Microbe-driven microrobots

Algae as natural carriers for drug-carrying systems have been rapidly developed in recent years. Zhong et al. used spirulina to build a drug-carrying system that was loaded with the chemotherapy drug adriamycin (DOX) for targeted delivery and fluorescence imaging-guided chemotherapy of lung metastases of breast cancer. The system demonstrated ultra-high drug-carrying efficiency and PH-responsive drug retardation [9]. Algae-nanoparticle hybrid microrobots are also very attractive for active in vivo delivery of therapeutic drugs. Zhang et al. attached antibiotic-loaded neutrophil-membrane-coated polymer nanoparticles to natural microalgae, thereby creating hybrid microrobots for active in vivo lung delivery of antibiotics, and tissue retention after intratracheal administration of antibiotics to a mouse model of sexually-exposed Pseudomonas aeruginosa pneumonia was excellent [10]. To address the issue of stable delivery of microrobots in the gastrointestinal tract, Zhang et al. reported an algal motility system that utilized persistent motility of natural microalgae in intestinal fluids to prolong retention time and enhance drug delivery in the gastrointestinal tract [11].

The use of bacteria to treat disease has a long history. Since bacteria are sensitive to various environmental conditions, they can be used for effective targeting. Bacteria can sense and move toward cancer cells or cell lysates, according to studies. One probiotic that is frequently utilized in clinical practice is Escherichia coli Nissle 1917 (EcN). Because of its parthenogenetic anaerobic characteristics, it can only live and proliferate in hypoxic areas of tumors. EcN can be engineered into a bacterial-based microrobot for molecular imaging, drug delivery, and gene delivery [12]. Xie et al. coupled adriamycin (DOX) to EcN via the acid-unstable linker of cis-aconitic anhydride (EcN-ca-Dox) to achieve anticancer drug bacterial-directed accumulation and acid-responsive release in tumors. The experimental results showed that the accumulation amount was much higher than that of the commonly used nanocarriers, which improved the antitumor efficacy [13].

Microrobot-targeted drug delivery using cells as carriers has also received much attention. Xu et al. introduced a sperm-driven micromotor-targeted drug delivery system, in which an anticancer drug (doxorubicin hydrochloride) was loaded into motile sperm cells, which were magnetically guided to in vitro-cultured tumor spheroids. Finally, the sperm cells were released to deliver the drug locally, minimizing the toxic side effects and the harmful drug in the accumulation in healthy tissues [14]. Macrophages, which are part of the mononuclear phagocytosis system, have sensory receptors that enable them to target cancer cells, showing promising results and potential for clinical application [15]. Zhang et al. used silica nanocapsules to successfully place DOX into macrophages to target tumors and effectively inhibit the spread of cancer [16].

4.2. Magnetically driven microrobot

Magnetically driven microrobot has a promising application because of their advantages, such as a high degree of freedom and low tissue destruction. It can be categorized into passive drug release and active drug release based on the operation of drug release. In the case of passive drugs, drug release is often performed with nanoparticles that are designed so that they respond to certain conditions (e.g., temperature, pH, etc.). Akolpoglu et al. proposed a magnetically controlled bacterial biohybrid by integrating magnetic nanoparticles loaded with photothermite and chemotherapeutic molecules, as well as nano-liposomes, onto Escherichia coli [17]. Capable of passing through biological matrices and colonizing tumor spheroids under a magnetic field, drug molecules were released on demand via near-infrared stimulation. An external magnetic field can directly trigger drug release or loading in cases of active drug release, in addition to acting as a power source for micro-propulsion. An anticancer medication (paclitaxel) was loaded into polymer-coated nanowires by Chen et al. using electrostatic interactions between the drug and the polymer to create a wired magneto-electric nanorobot. The device can be guided wirelessly and precisely to the target location by a rotating magnetic field and on-demand magnetoelectric-assisted drug release to kill cancer cells [18].

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4.3. Light-field mediated microrobots

Currently, light-field mediated microrobots are dominated by near-infrared light-stimulated drug release, and it is mentioned in 3.2 that Akolpoglu et al. have fabricated nanoparticle magnetic-field-driven robots for near-infrared-stimulated drug release. In addition, Nguyen et al. developed macrophage-based dual-targeting microrobots regulated by chemotaxis and an external magnetic field and can achieve precise spatiotemporal drug control at the tumor site under NIR laser irradiation [19].

4.4. Acoustically assisted microrobots

Acoustic field-driven microrobots are very promising for drug delivery due to the ability of acoustic waves to penetrate biological tissues. Garcia Gradilla et al. proposed a microrobot based on acoustically propelled and magnetically guided nanowires capable of releasing drugs in response to pH, with a model drug being released from protonated polymer fragments in acidic environments (pH < 4) [20]. Acoustic assistance can be used not only for actuation but also for active manipulation of micro formulations for drug release. A porous hollow microrobot with a spiral-loaded inner cavity, in which the drug is loaded, was proposed by Yan et al. In this one microrobot application of acoustic waves with a frequency of MHz can lead to disruption of the hollow spiral structure and drug release [21].

4.5. Stimulus-responsive hydrogel-assisted microrobots

Stimuli-responsive hydrogels are polymer-based delivery aids that can exhibit drastic changes in properties in response to small changes in environmental conditions (e.g., electric field, magnetic field, pH, etc.). This property can be used for targeted drug delivery. Kim et al. demonstrated a microrobot made of MNPs, poly (lactic-co-ethanolic acid) particles containing adriamycin, and hydrogels based on gelatin and polyvinyl alcohol (PVA) (PLGA-DOX particles). Through the use of an engineered, tailored electromagnetic actuation (EMA) and near-infrared (NIR) integrated system, the MNPs were targeted and extracted from the hydrogel microrobot. The residual PLGA-DOX particles may release anticancer medications, which could thereafter have therapeutic effects on the target lesion [22]. Li et al. fabricated a magnetically-activated pH-responsive hydrogel-based soft microrobot for targeted drug delivery, which, at different pH values showed different activity tendencies. A real anticancer drug microbead (PCL-DTX) was prepared and realized the movement of the target location as well as drug release [23].

4.6. 4D technology applications

With the development of 4D technology, micromachines have been created that combine microrobots and 4D printing. As a procedure that encourages structural transformation over time, 4D technology by definition enables materials to change shape over time in response to external stimuli. Researchers have developed various methods for stimulus-responsive microrobots, these stimuli include thermal, chemical, pH, light, and magnetic fields [24]. Xin et al. developed environmentally-adaptive shape-morphing microrobots (SMMRs) by programmatically coding for different swelling rates in pH-responsive hydrogels. More sophisticated manipulation of microscopic cargo (encapsulation and release) in biological applications empowers microrobots with shape deformation adaptation to dynamic environments [25]. This field is currently under rapid development.

5. Discussion

Microrobots have shown good application and great potential in the field of drug delivery. Currently, more research is focused on the driving method and drug release device. However, the current microrobot for drug delivery is still not perfect. First, achieving efficient navigation and localization is still a difficult task. The majority of medication-delivery microrobots are typically built to operate within the human body's circulatory system. However, because the human circulatory system has comparatively more complex characteristics than other systems, microrobots must have improved sensing and localization capabilities. Second, the biocompatibility of microrobots still needs to be explored, and adverse reactions, immune responses, and tissue damage need to be avoided. Finally, microrobots should be designed for disposal after use, either by surgical removal, self-destruct

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mechanisms, or natural excretion, and need to be innovated for safer disposal for the user. Researchers are constantly expanding their studies in new directions, and we believe that new and better motors and materials will soon emerge to help the application of microrobots in drug delivery.

6. Conclusion

The field of microrobotics has evolved rapidly in the last few decades, making it possible for microrobots to perform targeted delivery of drugs at the microscopic scale. Researchers have created a variety of braking methods for microrobot behavioral design, mentioned in the second part of this paper, which is categorized into endogenous power braking and external field braking. In the field of drug delivery, researchers have focused more attention on drug targeting and drug release, and have achieved good results from microorganisms, magnetic fields, light fields, acoustic fields, stimulus-responsive hydrogels, and other aspects of the relevant research. Even with the development of science and technology, 4D technology has also emerged in the field of microrobot drug targeting delivery.

Although microrobots still face many challenges in the field of drug delivery, a wealth of experiments by researchers have provided exciting progress in the current field of targeted drug microrobot applications. We believe that microrobots will achieve even more exciting results in the future.

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