Effects of Micro-/Nanorobots on Various Microbial Species

Subjects: Nanoscience & Nanotechnology

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One of the most pressing concerns to global public health is the emergence of drug-resistant pathogenic microorganisms due to increased unconscious antibiotic usage. With the rising antibiotic resistance, existing antimicrobial agents lose their effectiveness over time. This indicates that newer and more effective antimicrobial agents and methods should be investigated.

Keywords: antimicrobial ; bacterial infections ; drug resistance ; microrobots ; nanorobots ; autonomous treatment

1. Advantages and Disadvantages of Current Micro-/Nanorobots

People worldwide are struggling with various microbial infections that directly or indirectly cause deadly diseases. The development of antibiotic resistance, especially in bacteria-caused microbial diseases, makes it challenging to fight infectious diseases and results in severe morbidity and mortality in patients. With the help of developments in nanotechnology, micro-/nanorobots appeared as promising treatment tools in the biomedical and pharmaceutical fields. They exhibit tailorable activities according to their shapes, sizes, loads, and surface and physicochemical properties [1]. For example, micro-/nanorobots might reach the areas that are difficult to reach in the body, owing to their small size and different shapes. Hence, they can be useful in the future treatments of pathogenic bacteria-based biofilms [2]. Researchers have tried to prevent antibiotic resistance by providing specific targeting in antimicrobial studies with nanorobots, so it is thought that higher success can be achieved compared to traditional methods.

Although micro-/nanorobots have several advantages, such as real-time localization that can be provided by using common medical imaging techniques including X-ray, MRI, and ultrasound scans [3], there are some points to be critically considered before realizing their usage. The first of these is the delivery path of the given micro-/nanorobots. The navigation distance must be kept as short as possible and biological barriers should be kept in mind while designing, to deliver therapeutics to a targeted region efficiently [4]. Ensuring collective control is another issue. Creating collective micro-/nanorobots, which can act cooperatively and closely, while performing different tasks, would significantly improve their missions such as manipulation of objects, which would have high potential in the targeted biofilm disruption [5]. Another concern is the actuation or propulsion mechanism, which is divided into external control and chemical. In chemical energy-based motion, motion is achieved by converting chemical energy into mechanical or other forms of chemical energy. Although these micro-/nanorobots provide a high degree of autonomy with chemical energy, there is an increased risk of toxicity unless they are biocompatible [6]. Moreover, the fuel-loading capacity of the chemically catalyzed micro-/nanorobots is another factor limiting their long-term applications. The control of micro-/nanorobots by external fields enhances dynamic regulation and decision-making processes, such as motion and swimming speed control to release therapeutics at the right time and in the right place, and in addition, minimizes toxicity [7]. Finally, for establishing a long-term safety profile of micro-/nanorobots, the biodegradability, waste profile, immunogenic response, all, biocompatibility of the designed micro-/nanorobots should be carefully tested through animal and clinical trials [8]. In this manner, the studies carried out with FDA-approved nanoagents and/or materials make microrobots reliable and promising. Efficient retrieval after the operations is also crucial. For instance, magnetic micro-/nanorobots are recommended to collect back promptly via magnets to minimize damage to healthy tissues. Another important issue in microrobot design is the expenses. While external field-actuated microrobots can move without the need of fuel, for the use in the clinic, the real-life realization of them requires central medical facilities with expensive control systems, and professionally trained healthcare personnel. Thus, it is important to establish cooperation between the fields of medicine and engineering in order to produce microrobots that are biocompatible, therapeutically efficient, sustainable and affordable [9].

2. Recent Situation of In Vivo Antimicrobial Studies

In the dynamically developing field of micro-/nanorobots, their anti-microbial applications have also exhibited great enhancements. Consequently, the number of in vivo studies has been growing day by day. For example, in a study by Su et al. *P. gingivalis* periodontal disease in rats was demonstrated using a MnO_2-based microrobot. In another in vivo study, NIR-driven parachute-like nanomotors loaded with miconazole nitrate (PNM-MN) were injected subcutaneously into mice. Combined with the combination of pharmacological and photothermal effects for the treatment of mice infected with *Candida albicans*, the mice recovered completely and showed a therapeutic efficacy superior to other treatments [10]. In the study conducted with AuNP/mesoporous silica nanorobot containing antibiotics injected into the implantation site of mice infected with *S. aerus* bacteria, mice were treated within 10 min by magnetic activation without damaging any healthy tissue [1]. Similarly, a dextran-coated Fe_3O_4 microrobot was used for the treatment of mice infected with *S. mutans* [11]. Many in vitro studies have been conducted in the water environment or in a liquid that is used as fuel for the catalytic motion, however, their real in vitro efficiency remains unclear.

Considering the above-mentioned in vivo studies, and the advantages and disadvantages of micro-/nanorobots, soon researchers will be witnessing their promising antimicrobial applications in medicine. For example, treatment of resistive infections or biofilms in easier-to-reach body regions for micro-/nanorobots, such as gastrointestinal and urinary tracts, ear, nose, and throat [12], could be the starting point, particularly for the autonomous and magnetically actuated systems. In addition, the usage of an external actuation, such as light and/or ultrasound waves, together with the high-technology medical devices would let people develop highly targeted and efficient treatments for subcutaneous, periodontal, and implant-associated infections, owing to their penetration ability through the skin.

3. Application Routes, Limitations, and Future Perspectives

To reach success in the process of antimicrobial treatments, there are crucial elements that must be considered. Mainly, controlling the accumulation of antibacterial drugs at the site of infection, increasing bactericidal therapeutic efficacy, limiting the interactions of antibiotics with the healthy tissue, and reducing toxicity risks, and reducing the killing effect of antibiotics on commensal microflora are pivotal factors to consider when designing carriers for specific and sustainable release of antibiotics. To create better antibiotic delivery systems, an effective strategy would be to create a system that responds to stimuli in one of two ways. In these options, the system either reacts autonomously and recognizes the bacterial environment or is sensitized to certain physical elements. These methods will increase the effectiveness, targeting abilities, and effectiveness of antibiotic treatments while reducing their negative effects [13].

One of the main conditions leading to the acceleration of the evolution of MDR and the unselective killing of beneficial bacteria is the tendency of using traditional broad-spectrum antibiotics. A new start-up company, Eligo Bioscience®, reported that they have been working on creating antimicrobials, whose spectrum and activity can be designed by using CRISPR-Cas (“programmable gene scissors”) technology. The company, which is conducting in vivo studies with carrier devices such as nanorobots, has been focused on delivering RNA-guided nucleases (RGNs) for targeting specific DNA regions in microbial populations. The usage of programmable RGNs might trigger the emergence of alternative antibacterial techniques that impose direct evolutionary pressure at the gene level [14]. The design of delivery vehicles such as nanorobots will be important to create RGNs that can target other strains, such as multidrug-resistant pathogens.

In addition to the proven effects of micro-/nanorobots on bacterial species, a few studies mentioned that they could be also used for the treatment of viruses [15]. Studies with the SARS-CoV-2 virus, which threatens public health, have shown that micro-/nanorobot applications can be useful for destroying viruses. Micro-/nanorobots can make the transportation of antiviral medicines an effective and simple process due to their modifiable surfaces, speeds, and motion control. The ability to carry antiviral agents, particularly suitable for pandemic and epidemic viruses such as HIV, Herpes, Ebola, ZIKA, and Dengue will open the door to target-specific treatments of these viruses in the future [15][16].

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