Medical Hypotheses 102 (2017) 56–60

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Biodegradable microrobots for targeting cell delivery

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ARTICLE INFO

Article history:
Received 28 August 2016
Accepted 27 February 2017

ABSTRACT

These days, cell delivery is considered a potential method for treatment of many genetic diseases or tissue regeneration applications. In conventional cell delivery methods, cells are encapsulated in or cultured on biocompatible polymers. However, the main problem with these carriers is their lack of targeting ability. For tissue regeneration or many cell treatments, it is needed to deliver cells to a specific site of action. Magnetic microrobots based on industrial photoresists have been studied in literature for magnetically controllable carriers. However, there are some issues about biodegradation and removal of these microrobots from the body. In this paper, we hypothesis fabrication of new generation of biodegradable magnetic microrobots based on additive manufacturing methods to overcome this problem and to bring this evolving field to a new level.

Introduction

And background cell-delivery and therapy

Over last years, cell-based therapy has been considered as a potential method for treatment of various diseases including, hirschsprung's diseases [1], heart problems [2], brain disorders [3], central nervous system problems [4] and cancer [5]. Formerly, cells were administrated directly to the desired site of regeneration like infracted part of the heart [6]. However, it is reported that about 90% of cells die after direct injection [7]. Alternative approaches such as encapsulation of cells with biocompatible polymers were also studied [8].

Although above-mentioned methods reduce the probability of cell removal form the body, there is still a problem with conventional cell delivery approaches, which is lack of targeting. For many applications like cancer [9], spinal cord injury therapy [10] and cell transplantation to the heart we need targeting carriers to reach a specific site in the body and trigger the treatment process. However, these conventional cell carriers do not possess the ability to carry drugs or cells to the desired site. In order to overcome this problem, recently, microrobot based cell delivery is proposed.

Macro/microrobots in medicine

Nowadays robots are receiving increasing interest for minimally invasive medicine [11]. Significant advances are achieved particularly in centimeter-scale applications like gastrointestinal tract (GI) endoscopy [12] and robotic colonoscopy [13]. However, it is believed that robots with sub-millimeter dimensions (microrobots) can have a myriad of new biomedical applications in diagnosis and therapeutic [14].

Actuation of microrobots is one of their major limitations in design and fabrication. Given their submillimeter size, large-scale powering solutions are not applicable [15]. As a result, researchers have explored various off-board actuation methods like piezoelectric actuators [16], bacterial actuators [17,18], swimming tail actuators [19] and so on. In particular, electromagnetic driving method is among most interesting methods due to its unique advantages. It eliminates challenges like requirement of conductivity or transparency properties. Furthermore, electromagnetic field enables precise control of magnetic object by controlling a current and does not harm tissues even at relatively high strengths [20]. Consequently, many magnetically driven microrobots have been studied for in vitro and in vivo applications, such as microgrippers [21], microparticles [22] and helical swimmers [23].

Sub-millimeter devices can access hard-to-reach locations in the human body like urinary system [24] or inside the eye [25] while being minimally invasive. However, this scale at the same time places a strong constraint on their development. As we scale down, motion is governed by viscous forces and surface effects like electrostatics, which outweigh volumetric effects like weight and inertia [26]. Most micrometer-scale objects like bacteria move at

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http://dx.doi.org/10.1016/j.mehy.2017.02.015
0306-9877/

a low Reynolds number situation. A microrobot should possess a non-reciprocal motion in this situation to overcome viscous forces and move forward [27].

Helical propulsion and travelling wave propulsion are among envisioned approaches to mimic the behavior of bacterial and eukaryotic flagella in low Reynolds regimes [28]. The fundamental concept is to form the microrobot in an asymmetrical geometry like helical shape to enable generating the required non-reciprocal motion [29].

Fabrication of microrobots (materials and techniques) for cell delivery applications

Researchers have reported fabrication of such structures using different techniques including rolling-up [30], two-photon polymerization [31], Direct Laser Writing (DLW) [32] and 3D-printing methods [33].

The ideal microrobot should reach a targeted site, execute a predefined operation for a certain period of time and then be removed or degrade without side effects [34]. However, till now researches managed to mostly address the first two issues. In fact, considering fabrication limitations, widely established semiconductor/MEMS procedures and materials were used for microrobots and the biocompatibility was achieved using a covering layer like Titanium [35]. Although such microfabrication techniques provide a precise control over geometries, materials like photoresists are not designed to be biocompatible or biodegradable. As a result, using them in body can cause foreign body response (FBR), which in turn can lead to a chronic inflammatory for such non-degradable materials [36].

In addition, for microrobots to be an ideal cell-delivery scaffolds, they have to possess further biological properties including adequate cell-material interactions, architecture and biodegradation properties [37]. However, most industrial photoresists are epoxy-based materials without required biological properties. As an example, biological evaluation of SU-8 as a famous negative-tone photoresist showed inflammatory responses when used as an in vivo implant [38]. Such reactions can reverse the therapeutic goal of microrobots and adversely affect the already damaged tissue.

Consequently, providing biocompatible and biodegradable materials for microrobots that are at the same time compatible with microfabrication techniques can ease future applications of this evolving field of study. Precisely defined chiral architecture, biocompatibility, tunable degradation time and cell-adherence all at the same time are characteristics of a promising solution for ideal bio-microrobots.

Hypothesis

In this paper, we propose using biodegradable and biocompatible microrobots for targeting cell delivery applications. These days, cell delivery has been considered a promising method for treatment of wide range of diseases such as cancer, maternal defects, genetic abnormalities and etc. In many cases, the modified cells should be delivered into a specific site of action, however, most of the conducted researches are based on non-specific cell delivery approaches which diminishes efficacy of this method. In order to overcome this obstacle, recently, some researchers focused on using microrobots for targeting delivery of cells, using electromagnetic fields to control the pathway of cells attached to microrobots in the blood stream. However, the applied microrobots are not biodegradable and removal of such microrobots from the patient body creates new concerns. Thus, we propose using biodegradable and more biocompatible microrobots for targeting cell delivery.

Such biocompatible and biodegradable microrobots can be fabricated using polymeric nanocomposites containing magnetic nanoparticles in well-defined structures by 3D printing method. By choosing appropriate materials and design, this new generation of magnetically controllable microrobots would provide a novel approach in targeted cell-therapy.

Fig. 1 illustrates the main idea of using biodegradable cell carrier with the ability to deliver cells to a specific site and its removal from the body.

Evaluation of the hypothesis

Magnetic microrobots are shown to be capable of delivering a loaded drug or chemical [39]. However most of these microrobots do not possess basic requirements of cell carrier scaffolds like biocompatibility and biodegradability, which is a major drawback in their use for cell delivery applications. To provide the required biocompatibility, some researchers have coated their microrobots with a layer of Titanium dioxide or gold [40]. Although this method may solve the solution in the first sight, it has considerable disadvantages. First, these materials make the degradation process even harder and fabricated microrobots last longer in the body. Second, the covering layer should completely cover the microrobot during its whole life not to cause any immune response. Thus if during the fabrication or performance any part of the microrobot get exposed to body fluids, biocompatibility problems may occur.

Despite of all these problems, the idea of having precisely controllable carriers for drug and cell delivery is so important that many researchers are working on its development. Recently, Kim et al. proposed a method for targeting cell delivery using magnetic micro-robots. They employed two-photon lithography for fabrication of microrobots with lengths ranging from 154 to 160 μm. Using SU-8 negative tone photoresist, fabricated microrobots had pore sizes in the range of 10–21 μm to provide an appropriate architecture for culture of desired cells. Furthermore, microrobots were coated in 150 nm Ni as the magnetic material; followed by deposition of 20 nm of Ti to increase their biocompatibility. The adhesion, migration and proliferation of Human Embryonic Kidney (HEK) 293 cells on fabricated structures and their controllable behavior in presence of an external magnetic field; demonstrate the possible application of these microfabricated structures for in vivo cell delivery [41]. However, these microrobots lack the ability of self-removal from body via biodegradation.

As mentioned above, fabrication of the ideal microrobot especially for cell delivery applications has two main aspects: 1) Selection of the right material, 2) using a precise, fast and cost-effective fabrication technique. Here we evaluate our hypothesis from both points of views.

Material

The chosen material for this hypothesis should possess specific properties. Above all, it should be biocompatible and provide an appropriate substrate for adhesion and proliferation of cells. In addition, it should be biodegradable with a controllable rate of degradation, as it should maintain its structure during guidance to desired site of delivery. Finally, the material should be compatible with microfabrication techniques that are able to create micron-scale geometries in 3D.

There are some polymers showing biodegradable and biocompatible properties desired for this application. These polymers include natural polymers such as Gelatin [42], Chitosan [43], Alginate [44] and synthetic polymers such as PLA [45], PGA [46], PLGA [47], PCL [48] and PPF [49]. These materials have been widely