MEDICAL ROBOTS

Immune evasion by designer microrobots

Mahmut Selman Sakar

Recent work is unveiling the interactions between magnetic microswimmers and cells of the immune system.

Untethered mobile microrobots have the potential to contribute to the treatment of many diseases by enabling the targeted delivery of a drug to a particular tissue. Locomotion in physiological fluids at small scale requires special design considerations, and motile microorganisms have been serving as the primary source of inspiration. Seminal work has demonstrated the feasibility of actuating and steering flagellum-shaped magnetized microstructures, commonly referred to as microswimmers, using externally applied rotating magnetic fields (*1*, *2*). Since then, numerous articles have been published on the enhancement of the locomotion and drug-loading capabilities of these magnetic microswimmers. On their journey toward the target tissue, microswimmers are expected to surmount a number of barriers (e.g., blood-brain barrier, mucous membranes, and endothelium) without being detected as threats by the immune system. Hence, the rational design of microswimmers requires that the interplay between their navigation performance, therapeutic functionality, and immunogenic behaviors be deciphered to achieve safe, site-specific, and efficacious drug delivery (Fig. 1). Writing in this issue of *Science Robotics*, Yasa *et al.* (*3*) systematically investigated the interactions of magnetic microswimmers with the cells of the immune system. The presented methodology may serve as a benchmark for the evaluation of future robot designs for biomedical applications.

Extensive research in nanomedicine has shown that the physical properties of the particles can be tailored to either avoid recognition by the host or specifically inhibit or enhance the immune responses. Phagocytosis by macrophages, one of the primary clearance mechanisms of the innate immune defense, depends strongly on the size and geometry of the target particle (*4*). To explore the design space for nonimmunogenic morphologies, Yasa and colleagues systematically varied the helical turn number along the major axis of the microswimmers while maintaining the body volume and examined the interactions

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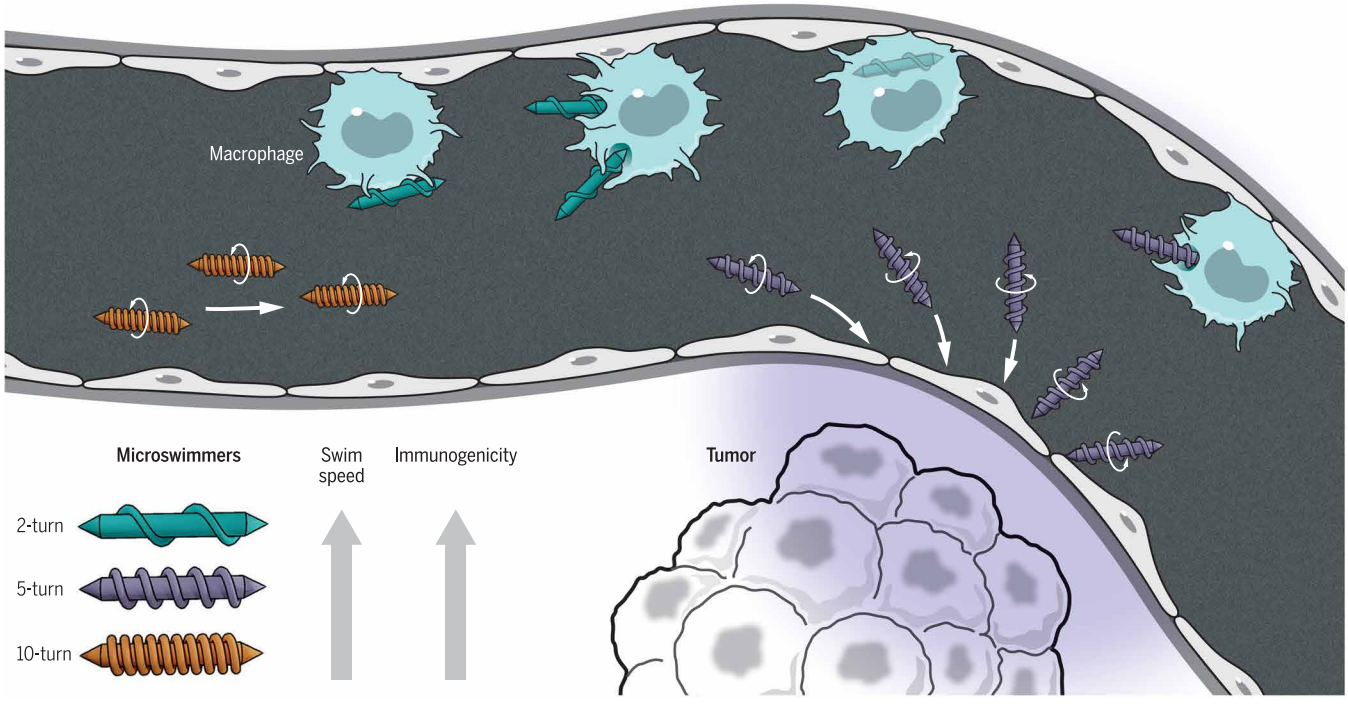

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Fig. 1. Optimization of microswimmer shape for targeted drug delivery. Illustration of a future use case for the medical microrobots emphasizing an important design tradeoff. Double-helical magnetic microswimmers with filled internal cores are 3D-printed as concentrated drug-carrying bodies. Three morphological derivatives of the same design are tested with the same body length, outer diameter, and body volume, only varying the number of helical turns along the major axis (2-turn, 5-turn, and 10-turn). Two-turn microswimmers exhibit the best locomotion performance, yet they were preferentially targeted by the macrophages. Increasing turn number deteriorates swimming performance while reducing immunogenicity, presenting a compromise between speed and physical interactions with the immune system.

of mouse macrophage cell lines with the microswimmers using electron, optical, and confocal microscopy. Hundreds of time-lapse movies of macrophages engulfing surface-bound microswimmers were recorded and analyzed for revealing the impact of the robot morphology. Notably, the findings of this study suggest that a shape that is optimized for enhancing locomotion performance can make the microswimmers immunogenic (Fig. 1). Immunogenicity of the microswimmers was investigated by presenting them to primary mouse spleen cells that consist of a variety of white blood cell populations, including macrophages and lymphocytes. The results show that microswimmers with superior mobility induce higher production of interleukin-12, a pivotal cytokine with important regulatory functions in innate and adaptive immunity.

There are established techniques to camouflage particles by modulating the physicochemical properties of their surfaces. Harnessing these techniques in the development of the microswimmers may decouple the design for navigation and operation from immune response considerations. Yasa *et al.* used a classic strategy, functionalization of the particle surface with poly(ethylene glycol) (PEG), or PEGylation, to provide a hydrating layer around the structure and avoid phagocytosis. Previous work has shown that biomimetic coatings, such as CD47 peptides or cell membranes extracted from leukocytes and red blood cells, misguide macrophages to identify the foreign particles as self (*5*). Tuning surface charge and local curvature are alternative routes for making microswimmers challenging targets for the immune system. Conveniently, microswimmers are printed using two-photon polymerization, a technique that enables precise control over shape and topography. From a robotics perspective, microswimmers are actuated devices, and their mobility may be leveraged to actively comprise the effectiveness of the phagocytosis process and minimize unwanted immunogenic responses.

The microswimmers fabricated by Yasa and co-workers are rigid structures. Immune cells can sense whether they are exposed to soft or rigid substrates; thus, mechanobiology constitutes another dimension in the design space (*6*). A soft microswimmer may exhibit a drastically different behavior during the course of phagocytosis, from recognition to the degradation processes. Incidentally, soft microswimmers engineered from natural hydrogels have numerous benefits for targeted therapies such as enzymatic biodegradability, tunable chemistry, and high loading capacity for pharmaceuticals (*7*, *8*). Furthermore, flexible microswimmers fabricated from soft and smart hydrogels display adaptive locomotion through autonomous shape shifting (*9*).

Cancer immunotherapy has revolutionized the field of oncology. There is a growing realization that the targeted delivery of immunomodulatory compounds to immune cells using particles can organize selective eradication of cancer cells (*10*). Yasa and co-workers show that the internalization of microswimmers can be exploited to combine magnetic manipulation with the autonomous locomotion of the immune cells. This is a drastic deviation from the original stealth approach that is explored in the first part of the article and instead motivates joining forces with the immune system against tumors. The new challenge is designing the microswimmer that has the greatest potential for phagocytosis and subsequent operations of the biohybrid system. Although the objectives are conflicting, the same methodology will serve for the realization of microswimmers that are companions to the immune system. Considerable efforts will be needed to validate that augmenting the immune cells with engineered structures does not impede their immunotherapeutic functions.

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