MEDICAL ROBOTS

Robotic self-modulation enhances implantable long-acting drug delivery devices

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Integrating fibrotic capsule sensing with soft robotics may boost long-term performance of implantable drug delivery devices.

Long-acting (LA) drug delivery implants play an important role in medicine because they offer a solution for sustained and controlled release of medications, reducing the need for frequent dosing and improving patient compliance. These implants hold great potential for preventing and treating chronic conditions and provide therapeutic benefits over an extended period, enhancing the overall drug effectiveness. Upon deployment, LA drug delivery implants trigger foreign body response (FBR), which involves inflammation, tissue remodeling, and fibrosis (*1*). In numerous instances, FBR leads to a complete fibrotic encapsulation of the implant, which could compromise its function and longevity. Sustained low-dose LA devices relying on drug diffusion across nanoporous or nanofluidic membranes are unaffected by fibrotic encapsulation (*2*). In contrast, fibrosis can substantially influence the performance of LA systems that use convection to achieve drug delivery across micro- and macro-orifices. This is the case of infusion pumps and intrathecal drug delivery systems that rely on catheters to convectively deliver medications into the body and specific tissues. Fibrotic encapsulation may also impair the function of drug delivery implants designed for pulsatile drug delivery (*3*) or emergency medicine, requiring larger boluses of medication to be delivered within the body within seconds or minutes. The formation of fibrous tissue around the orifices can obstruct drug delivery and alter the release profile, leading to unpredictable and suboptimal therapeutic outcomes.

Various strategies to curb the FBR, mitigate fibrotic encapsulation, and maintain the functionality of drug delivery systems are under investigation. These include surface modifications, FBR-targeting agents, and biomimetic materials and coatings (*4*, *5*). However, individually, these approaches show mixed success and fail to address the complexity and progression of the FBR. A combinatorial approach to slow fibrous encapsulation, modulate local tissue microenvironment, and tailor the pressure of drug ejection based on patient-specific factors may be the optimal strategy to enhance device longevity and performance. However, dosing adjustment based on temporal changes in fibrotic tissues surrounding the implants is largely unexplored, likely because of the lack of approaches for continuous monitoring of the FBR in real time using physiological signals.

Reporting in *Science Robotics*, Beatty *et al.* present a self-adaptable implant capable of sensing fibrotic tissue formation and, in response, adjusting drug release via pneumatic soft robotic actuation to maintain consistent dosing from microporous membranes (*6*). Termed the FibroSensing Dynamic Soft Reservoir (FSDSR), the implant incorporates a microporous membrane for drug delivery, a sensor that can continuously monitor the interface between the membrane and

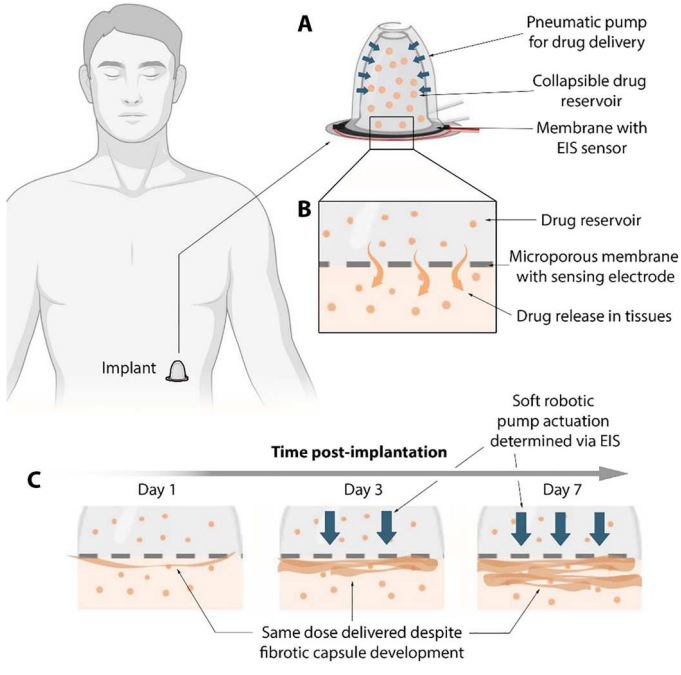

Fig. 1. Self-adjusting implantable drug delivery device aided by fibrotic tissue sensing. (**A**) Schematic of the soft robotic implant structure integrating a pneumatic pump to actuate delivery of the drug via convection, a collapsible drug reservoir containing the drug solution, and a microporous membrane with integrated sensor to detect fibrotic capsule formation via EIS. (**B**) Close-up illustration of the abiotic/biotic implant/tissue interface and drug release through the implant's microporous membrane. (**C**) Progression of the fibrotic encapsulation on the implant after implantation and self-adjusted drug release actuation based on EIS output to sustain consistent drug dosing despite the fibrotic tissue barrier.

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surrounding tissues, and a soft robotic pneumatic system for the delivery of a drug solution from a collapsible reservoir (Fig. 1A) (*7*). Integrated within the microporous membrane (Fig. 1B), the sensor uses highly conductive acrylic electrodes to monitor the fibrotic capsule development via electrical impedance spectroscopy (EIS). EIS is a powerful noninvasive technique that enables the measurement of materials properties by measuring the resistance that an alternating electrical current experiences when passing through the material at different frequencies. EIS is clinically used in cancer diagnostics and has applications in various biomedical use cases including in vivo sensing (*8*). Using EIS, the FSDSR could detect changes in the cellular environment in tissues adjacent to the membrane and the formation of fibrotic capsule within the membrane pores, validating the device's ability to sense and monitor the progression of fibrotic capsule formation.

Beatty and colleagues used real-time fibrotic tissue data to tailor actuation of the implant's soft robotic pneumatic pump, achieving consistent drug delivery regardless of the increasing impediment posed by the growing fibrous tissue (Fig. 1C). Using the *k*-nearest neighbor (KNN) learning algorithm, they showed that machine learning can drive autonomous control of the drug delivery system based on real-time EIS data. Furthermore, aided by simulations in silico, they determined that the FSDSR could, in principle, function autonomously for long-term drug delivery in vivo. It is likely that the development of a practical closed-loop system would require more advanced algorithms, such as neural networks, to adjust drug delivery based on sensor readings and incorporate additional physiological signals. In addition, although the FSDSR shows success in monitoring fibrotic capsule progression and adjusting drug delivery in rodents in a laboratory setting, limitations remain in replicating the FBR in humans. For this, future research is required to investigate FBR in relevant animal models and eventually in a clinical setting. Moreover, translation will require selection and testing of a clinically relevant drug, such as insulin, which requires time-controlled administration.

The FSDSR technology displays various innovative aspects. The ability of the implant to self-adapt based on the time evolution and continuous remodeling of the surrounding tissue microenvironment sets this system apart from conventional passive drug delivery systems. Thus far, the potential for self-adjustment is only attainable in biological systems for the delivery of cells (*9*) and organoids (*10*). The ability of the FSDSR to monitor its own membrane deformation provides valuable feedback on the performance of the implant. This feature offers improvements to existing soft robotic drug delivery devices. Last, the use of machine learning in the implant represents a notable example of the potential for artificial intelligence in medical device development and function, which is an increasingly important area of research (*11*).

Overall, the FSDSR holds promise in overcoming fibrotic capsule diffusion barriers and ensuring consistent drug delivery in a wide range of medical device applications. Importantly, the sensing technology is highly flexible and could enhance the life span and function of existing implantable clinical devices. As an example, the sensor could potentially be integrated within the outlet of transcutaneous catheters of insulin pumps and intrathecal drug delivery devices, providing feedback regarding the fibrotic tissue ingrowth in the catheter lumen and permitting delivery adjustment. The technology by Beatty and colleagues sets the stage for the development of future implantable robotics for drug delivery.

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