MICROROBOTS

Robotic probes at the cell scale

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The miniaturization of robotic tools and probes enables the fundamental study of mechanical properties of cells and tissues.

Historically, most studies on cell biology have been approached from the perspective of biochemistry. However, it is now well understood that the physical properties of the cells are as important as their biochemical characteristics, and, most often, the two are interlinked (*1*). Likewise, it is known that individual cells belonging to the same cell population can have distinct characteristics (*2*), affecting the functionality of the entire population or even the organism. These heterogenous cellular characteristics are now recognized thanks to the progress that has been made in the miniaturization of devices and probes, opening up innovative avenues for research at the cell scale. In their latest research work, Mohagheghian *et al.* (*3*) have developed a magnetic microrobot capable of locally probing the mechanical properties of cell populations and single cells as well as measuring the traction that they experience. The capabilities of this magnetic microrobot were demonstrated with a colony of tumor cells as well as in zebrafish and mouse embryos.

Within the cell, there exists a network of filaments, the cytoplasm, the cell membrane, and the cortex, whose mechanical properties can be modulated by the cell (*4*, *5*). These complex intracellular cell mechanics are coupled with the extracellular matrix to mechanically respond to the cues of the cell's microenvironment. This dynamic mechanical system is critical in physiological processes, such as cell division and migration, as well as in pathological processes, such as vascular diseases and cancers. Therefore, the ability to probe these mechanical properties and traction experienced by cells is of great value for basic cell biology.

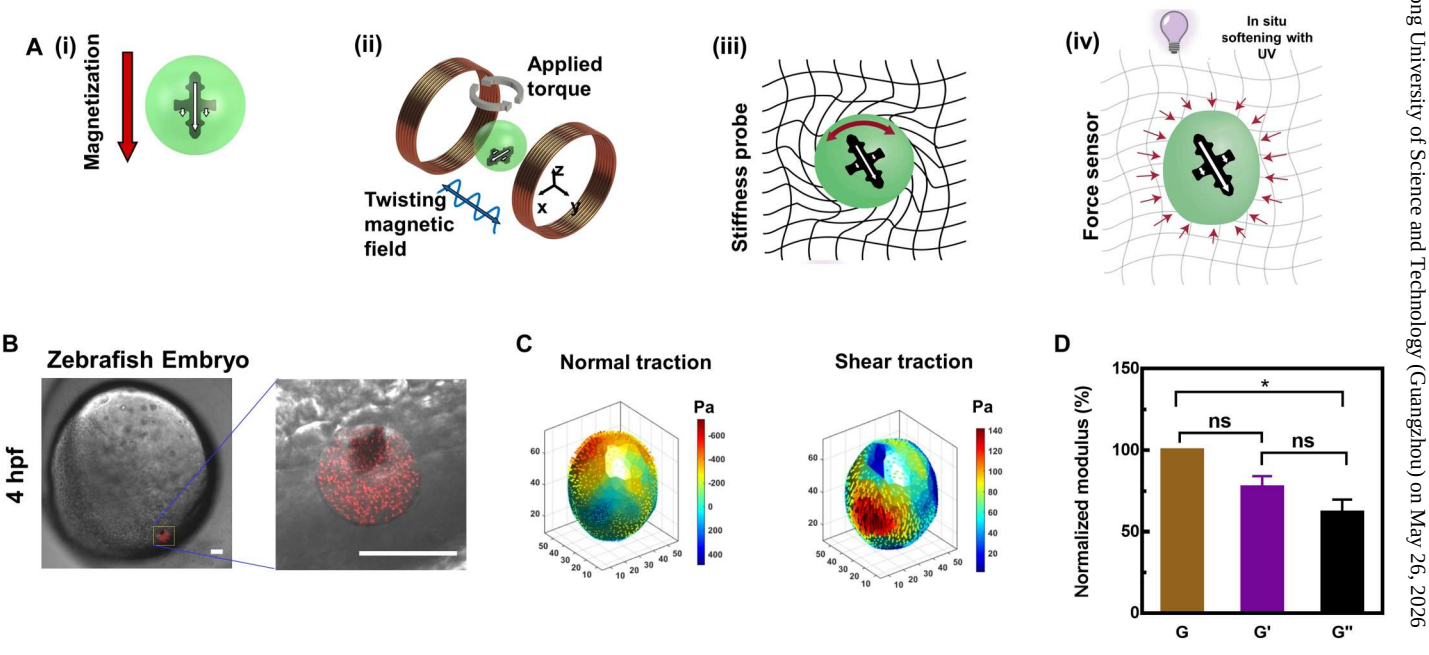

Fig. 1. Quantifying cell and tissue mechanical properties and exerted traction using microrobots. (**A**) The microrobot working principle. A microrobot was developed by incorporating a ferromagnetic microcross within a gel. Under the influence of an external twisting magnetic field, the microrobot could be rotated within a tissue of interest to measure the modulus of the microenvironment. The microrobot was subsequently softened with UV light to measure the deformation due to external traction exerted by cells. (**B**) The microrobot was injected into a zebrafish embryo (scale bar, 50 μm). hpf, hours post fertilization. (**C**) Normal and shear traction exerted onto a probe inside a zebrafish embryo by the surrounding cells. (**D**) Experimental normalized moduli (complex modulus *G*, storage modulus *G'*, and loss modulus *G''*) for zebrafish embryos showing larger storage modulus than loss modulus. ns, not significant.

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Mohagheghian and colleagues followed from their previous work (*6*) of using soft elastic microgels to quantify traction in cell colonies. In the current work, they fabricated a ferromagnetic microcross that was incorporated within a polyethylene glycol microgel containing fluorescent nanoparticles using a microfluid device. The microgel with the microcross was subsequently magnetized with a magnetic resonance imaging machine to eventually develop the magnetic microrobot probe (Fig. 1A). The microrobot was used for measuring mechanical stiffness by applying a magnetic field that rotated the microgel, and the response of the cells to this rotation was measured. The researchers could also measure traction when the microgel was softened by ultraviolet (UV) light, thereby permitting cells or tissues to exert a traction that could be quantified by the probe.

The researchers initially quantified the shear modulus of a tumor cell colony in vitro. A mouse melanoma B16-F1 cell colony was cultured with the microrobot probes on rigid glass substrates and glass substrates covered with 1-kPa polyacrylamide gels. They showed that after exposure to the magnetic field, there was greater angular rotation of the probe in the colonies cultured on 1-kPa gels than in those cultured directly on rigid substrates, and from these data, they could quantify the complex shear modulus, storage shear modulus, and loss shear modulus. They also softened the microgels with UV light to quantify the traction generated by the cell colony on the microrobot probe.

Mohagheghian and colleagues subsequently used the microrobot probes to quantify stiffness and traction in zebrafish embryos (Fig. 1B). The probes were injected into the embryos, and, using a similar technique as the tumor cell colonies, they could measure mechanical properties and traction exerted. They observed that the embryos exhibited viscoelastic responses to the applied shear stress, and a dominant storage modulus was measured. They were also able to measure normal traction, with large traction of about 250 Pa detected in the embryos, whereas smaller traction of about 50 Pa were detected at the embryo-yolk boundary, indicating the heterogenous nature of internal traction generated by cells at various locations of the embryo. The researchers also used the microrobot probes to measure traction in a developing mouse embryo. They used microgels without the magnetic microcrosses, which were injected into the embryos and subsequently observed over a 27-hour period. They detected normal traction of about 1 kPa. They also detected large tensile and compressive traction, indicating the ability of the embryo to exert pushing and pulling traction during the blastocyst stage.

There are several limitations in the use of such microrobot probes. For example, errors could be obtained because of high variability in the control of the dimensions of the gel sphere and the microcrosses, as well as their positioning at the center of the microgel. Device calibration becomes a requirement when high variability is present. Moreover, combining two measurement types (modulus and traction) for one probe could also generate errors, particularly because the microgel needs to be softened with UV light. Another important limitation is size because Mohagheghian *et al.* could not internalize microrobots with magnetic crosses in mouse embryos. Eukaryotic cells typically have smaller diameters than mouse embryos; thus, device miniaturization for future intracellular applications is a challenge. Simple biological experiments could be required from a large number of cells; thus, the sensing and actuation principles of the microrobots should be expanded to study a larger number of cells inside a population. Overall, however, the use of these microrobots as sensors to study cell populations could be valuable in observing the dynamic nature of cells during development.

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