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A novel perspective on the regulation of cardiac cell beating: cardiac cell under mechanical stimulation acts as "cell activation button" to activate adjacent cardiac cell

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Abstract

The regulation of cardiac cell beating is of great significance for understanding cardiac coordination mechanisms and the treatment of cardiovascular diseases. Inspired by this natural "cell regulates cell" mode in which sinoatrial node cells regulate atrial myocytes, this study presented a novel method to replicate this behavior in vitro through mechanical stimulation. Primary cardiac cells from Sprague-Dawley rats were isolated, cultured in 2D substrates, and applied to precise mechanical stimulation by developing a micro-manipulation platform. We demonstrated that a mechanical probe can act as an external activation device for quiescent cardiac cells, transforming them into "activation cells" capable of activating adjacent "target cells" through bioelectrical coupling. Calcium imaging with Fluo-4 probes revealed that this "cell activates cell" mechanism relies on mechano-electric feedback and calcium-mediated signal propagation via cell junctions. Our findings provide a non-destructive strategy to regulate target cardiac cell, deepen insights into the mechanical modulation of intercellular communication, and offer a framework for studying arrhythmias linked to abnormal cell-cell communication. This work combined mechanical intervention with biological signaling, advancing potential applications in cardiovascular therapeutics.

Introduction

Heart, one of the most central and complex organs in humans, plays an irreplaceable role in maintaining the normal operation of life activities. The pumping function of the heart depends on the coordinated contraction of cardiac cells. Under physiological homeostasis, cardiac cells are a highly cooperative functional syncytium, relying on spontaneous electrophysiological activities and intercellular signal transduction, and to ensure the overall synchronous contraction and relaxation function of the heart [1–4]. Cardiac cells can adjust their beat behaviors to specifically respond to external stimulation [5–8]. Therefore, developing external regulation methods of cardiac cell beat is important, which can help us understand the coordination mechanism of the heart system. It may also provide ideas for the exploration and treatment of cardiovascular diseases.

In vivo, sinoatrial node cells regulate atrial myocytes by transmitting rhythmic bioelectrical signals through natural intercellular communication [9–11]. Replicating this "cell activates cell" mode in vitro could provide a non-destructive approach to regulate cardiac cell beating. However, traditional stimulation methods—such as

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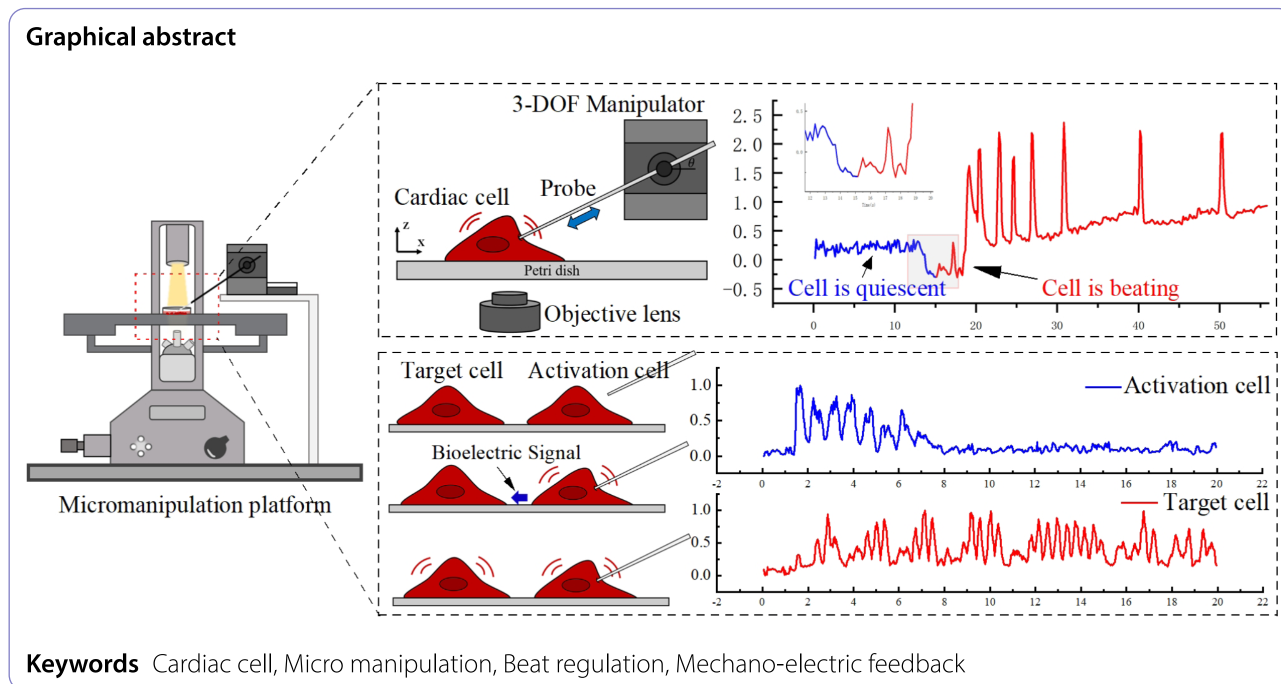
Graphical abstract



Keywords Cardiac cell, Micro manipulation, Beat regulation, Mechano-electric feedback

electrical, drug, or optogenetic techniques—often generate diffuse stimulation fields that affect adjacent cells [12–14]. Mechanical stimulation offers spatial precision, but existing methods (e.g., substrate stretching or shear force application) risk altering the cellular microenvironment (substrate deformation), potentially interfering with target cells [6, 15–16].

To address these limitations, this study developed a novel micro-manipulation platform that enables precise mechanical stimulation of individual cardiac cells. By focusing stimulation signals on a single cell, we aimed to transform quiescent cardiac cell into "activation cell" capable of activating adjacent "target cell" through natural bioelectrical conduction. This approach depends on mechano-electric feedback, a fundamental property of cardiac cells, to achieve targeted activation without other damages.

Specifically, we isolated primary cardiac cells from Sprague-Dawley rats and cultured them on 2D substrates to minimize the interference of substrate deformation. Using a designed mechanical probe, we demonstrated that local mechanical stimulation can induce excitability in quiescent cells. Furthermore, we demonstrated that activated cells transmit signals to adjacent cells via intact cell junctions, a process visualized using Fluo-4 calcium ion fluorescent probes.

This "cell activates cell" mode not only reproduces natural cardiac coordination but also provides insights into arrhythmogenic mechanisms caused by abnormal intercellular communication.

Materials and methods

Isolation and culture of cardiac cells

Primary cardiac cells were isolated from 1-2-day-old Sprague-Dawley rats (Guangdong Medical Laboratory Animal Center, China). Briefly, ventricular tissues were minced into 1-mm^3 fragments and digested with 0.25% Trypsin-EDTA at 37 °C for 10 min with agitation. Repeat the above step 7–8 times. Cell suspensions were filtered through a 70-μm sieve, centrifuged (1000 rpm, 5 min), and resuspended in DMEM containing 10% fetal bovine serum and antibiotics (10 KU/ml penicillin, 10 mg/ml streptomycin), and cultured in a 5% CO_2 incubator at 37 °C.

Before plating the cells, we strategically controlled the density of cells plated on 2D substrates to range between 50,000 and 100,000 cells/per cm^2, which was determined by counting with a standard hemocytometer. This range of cell density results in an approximate spatial separation of 0-300 μm between individual plated cells. Quiescent cells (no spontaneous beating within 3 min) were selected for experiments.

Micro-manipulation platform for mechanical stimulation of cardiac cells

This study developed a micro-nano manipulation platform for mechanical stimulation of cardiac cells, as shown in Fig. 1. This platform consists of an inverted optical microscope (Olympus, IX −53); An electric X-Y stage (Proscan III, prior) with a motion range of 120-mm×80-mm and a positioning resolution of 0.04-μm. A camera (Basler, acA640-120gm) is connected to

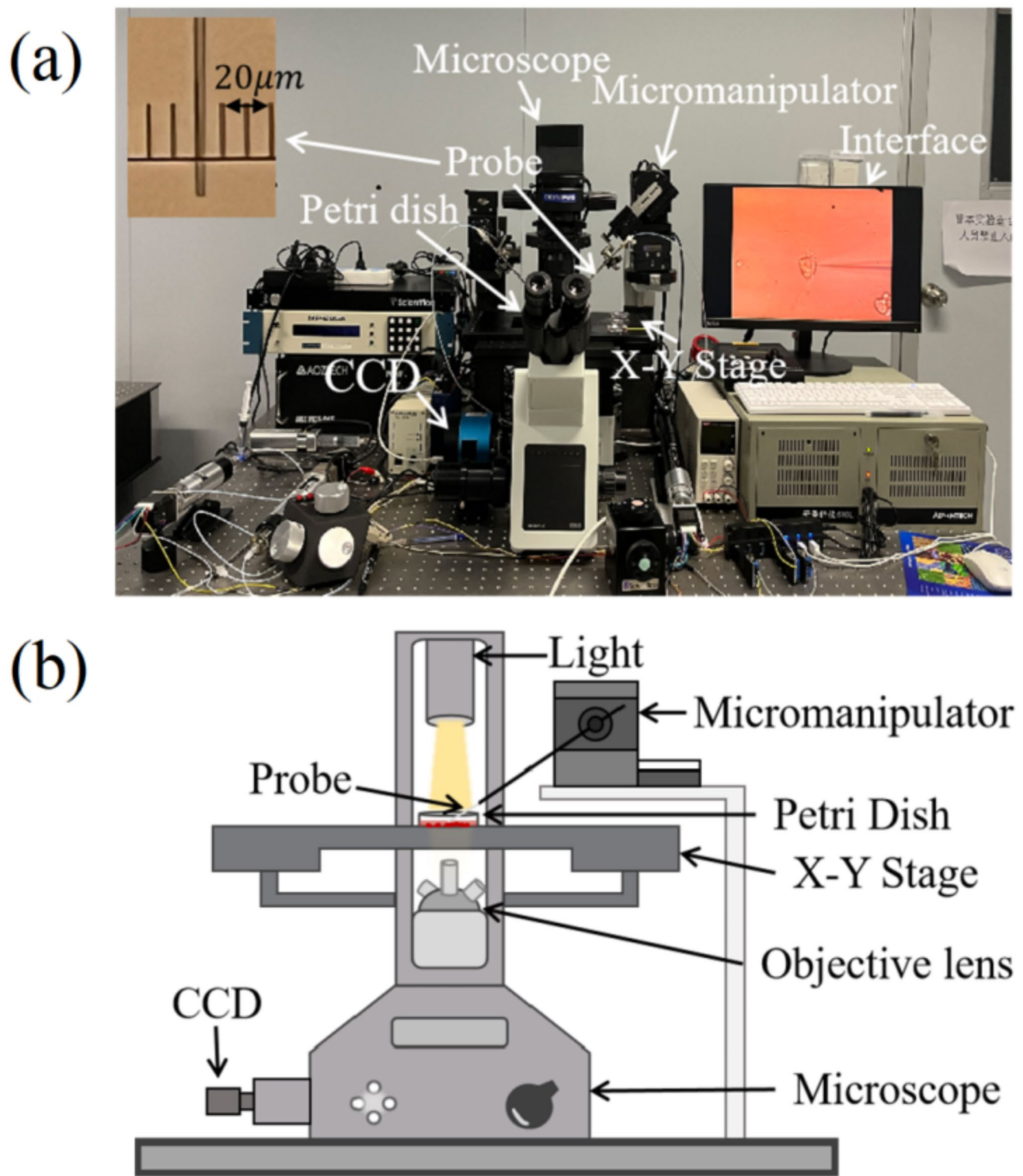


Fig. 1 The micro-manipulation platform for mechanical stimulation of cardiac cells. The whole experiment is performed on this platform. (**a**) and (**b**) are the physical diagram and schematic diagram of the micro-manipulation platform respectively. The platform mainly consists of an inverted microscope with an X-Y electric stage, a micromanipulator and a camera. Through the real-time feedback captured by the camera, the stage is controlled to move cardiac cells to the target position, and the 3-degree-of-freedom micromanipulator loaded with a mechanical probe is controlled to apply the mechanical stimulation of the cardiac cells

the microscope for visual feedback.A micromanipulator (Scientificia, PatchStar) with a motion range of 25-mm and a positioning resolution of 0.04-μm is installed on the right side of the microscope for manipulating the mechanical probe. The mechanical probe (2–5 μm) is fabricated from a borosilicate glass micropipette (Sutter, B100-75-10; outer diameter: 1.0 mm) as shown in Fig. 1(a) (Specific steps and forging process are described in S1).

In addition, there is an industrial computer used to control multiple motion control devices. Through real-time capture and feedback by the camera, the electric X-Y stage is controlled to move the cardiac cells, and combined with the manipulation of the mechanical probe by the 3-degree-of-freedom micromanipulator, mechanical stimulation of the cardiac cells is achieved.

Analysis of the movement behavior of cardiac cells

The frame difference method was used to quantitatively analyze the movement of cardiac cells, and the analysis process was completed in the MATLAB environment. The specific process is as follows:

1) First, recording the continuous video sequence in the experiment and defined the regions with significant intensity changes on the cell edge and inside as the regions of interests (ROIs) for analysis. Then, calculating the pixel differences between adjacent frames within the regions of interest:

$$D(t) = |I(t) - I(t-1)|$$

where $I(t)$ is the image of the t-th frame.

2) Then, the difference images within the ROI region were thresholded to remove background noise:

$$D_{th}(t,x,y) = \begin{cases} D(t,x,y), & D(t,x,y) > T \\ 0, & D(t,x,y) < T \end{cases}$$

3) Finally, the average physical displacement within the ROI region of the cardiac cell was calculated:

$$\Delta X(t) = \frac{1}{N} \sum_{(x,y)\in R} D_{th}(t,x,y) \times p$$

where N is the number of pixels within the ROI region, and p is the actual physical distance corresponding to the pixel.

Through the above video processing method, we can accurately track and extract the movement behavior of cardiac cells within the region of interest.

Calcium imaging of cardiac cells

The Fluo-4 calcium ion fluorescent probe was loaded into the cardiac cells in the experiment to monitor the changes of free calcium ions in the cells during the process. First, the Fluo-4 AM stock solution was prepared into a 2-μM working solution with phosphate buffered saline (PBS). For the cardiac cells in the experiment, the culture medium was removed and washed three times with PBS. Then, the prepared working solution was added to the culture dish until it covered the cell surface, and the culture dish was placed in a cell incubator (culture conditions: 5% CO_2, 37 °C) for 30–60 min. Under a fluorescence microscope, the culture dish was irradiated with blue emission light with a wavelength of 516-nm. When strong green fluorescence flashes were observed in the beating cells, the culture dish was transferred to the micro-manipulation platform to perform the subsequent experiments.

Results and discussion

The mechanical probe can become an external activation device for the cardiac cells

To achieve the "cell activates cell" regulatory mode, we first verified the ability of local mechanical stimulation to independently activate quiescent cardiac cells. The study employed the micro-manipulation platform with a mechanical probe to apply mechanical stimulation to selected quiescent cardiac cell. A significant change in cell beat behavior was observed, as shown in Fig. 2 (Supplementary Video S1).

The glass probe with a diameter of 5-μm was installed on the manipulation platform. The platform was equipped with a 3-degree-of-freedom robotic arm, which was set at a 45° angle. Figure 2(a) shows the position of the glass probe above the cardiac cell at an oblique angle. The probe approaches the middle position of the quiescent cell along the direction of the probe tip, moving at a speed of 5-μm/s. Finally, it makes contact with the cell. As shown in Fig. 2(b), a single cardiac cell is squeezed by the probe to produce a local deformation.

Throughout the experiment, the response of the cardiac cells was monitored by an inverted microscope and time-lapse video recording. The local contour of the cardiac cell was taken as the region of interest in this study, and the frame difference method was used to detect the average displacement of this region relative to the initial state of the cell. This analysis was performed during the entire stimulation process, with the x-axis defined as the positive direction. Figure 2(c) shows the typical average displacement of the local contour of the cardiac cell as

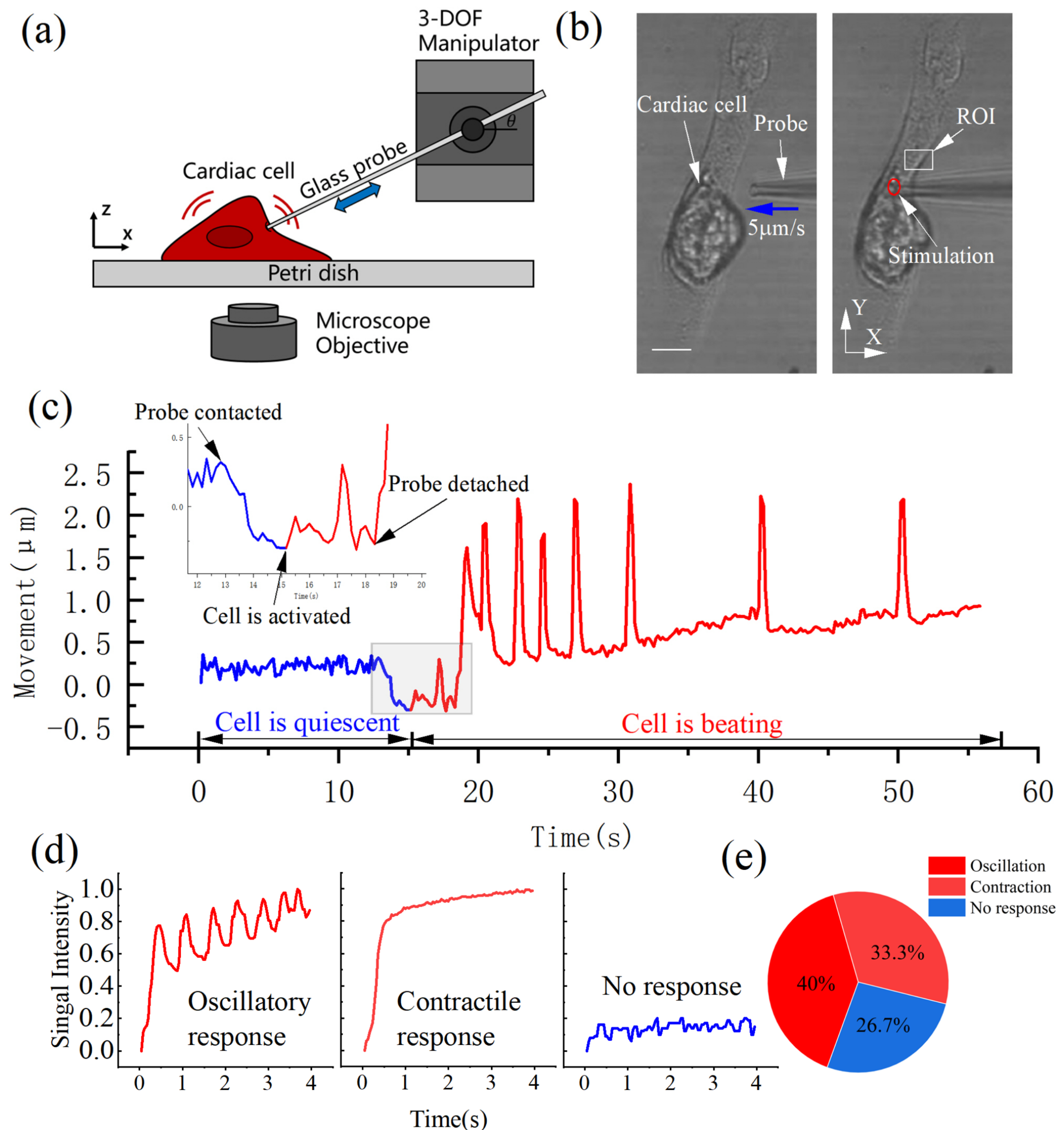


Fig. 2 The mechanical probe can act as an external activation device for cardiac cells. (**a**) Schematic and (**b**) experimental image of mechanical stimulation using a mechanical probe. (**c**) Average displacement of the cell contour under stimulation: blue curve (quiescent state) and red curve (activated state). (**d**) Three mechanical response phenotypes observed in quiescent cells. (**e**) Percentage distribution of response phenotypes ($n = 30$ cells; 22 activated, 8 non-activated). Chi-square test confirms statistical significance (*$P < 0.05$). Scale bar: 30-μm

a function of time, which includes the probe stimulating the cell and the corresponding cell activation situation. When the probe contacts and squeezes the cell to a certain extent (12–14 s), the quiescent cell begins to beat. At this time, the probe is withdrawn. Before the probe leaves the cell (12–18.5 s), the beating of the cell is still hindered by the probe (two smaller peak displacements at 15s and 17s). When the probe leaves the cell surface, the cell is completely released and produces a stress-beating response (19–31 s). After the stress adjustment of the cardiac cell, it begins to beat stably with a period

of 10s (31–55 s). This indicated a successful mechanical activation.

Mechanically stimulated cells exhibited two distinct phenotypes: Responding phenotype (with spontaneous beating behavior) and non-responding phenotype (without spontaneous beating behavior), as shown in Fig. 2(d). The responding phenotype is divided into two types: the first is the typical oscillatory response ($n = 12/30$ cells), that is, the quiescent cardiac cell begins to contract and relax periodically; the second is the contractile response ($n = 8/30$ cells), that is, the quiescent cardiac cell does not beat periodically, but only contracts one time. Non-responding phenotype ($n = 8/30$ cells) means that the quiescent cardiac cell stays still all the time. Statistical analysis revealed a significant activation rate (73.3%, 22/30 cells, χ^2 test, $P < 0.05$, Fig. 2e).

To quantify the mechanical threshold for activation, we analyzed the local deformation of cardiac cells during probe stimulation. The transverse diameter of quiescent cells ranged from 10 to 20 µm, when the probe-induced deformation reached 5 –20% of the cell diameter (0.5–4 µm), cells exhibited responding phenotype (Fig. 2c). Smaller deformations (5 –10%) predominantly induced oscillatory responses (periodic beating), whereas larger deformations (> 20%) led to contractile responses or irreversible damage (Fig. 2c –2d). These results suggest that mechanical sensitivity thresholds vary with deformation magnitude, likely reflecting differential activation of mechanosensitive ion channels or cytoskeletal remodeling pathways.

Control experiments confirmed that unstimulated cells remained quiescent, excluding spontaneous activation artifacts. Repeated stimulation of the same cell had the consistent activation thresholds, confirming preserved mechanical and metabolic functionality (Figure S2, Supplementary Video S6). Live/dead staining demonstrated high post-stimulation viability in activated cells after appropriate mechanical stimulation (Figure S3).

These results indicate the mechanical probe as a precise, low-destructive device for cardiac cell activation—a prerequisite for subsequent “cell activates cell” experiments.

Mechanically activated cardiac cell can act as “cell activation button” to activate adjacent cardiac cell

In this section, we explore the hypothesis that a mechanically activated cardiac cell (“activation cell”) can propagate excitatory signals to adjacent quiescent cells (“target cells”), mimicking natural intercellular communication [17, 18]. Using a spatially controlled mechanical probe, we demonstrate that local stimulation of a single cell can induce synchronized activation of adjacent cells, achieving a “cell activates cell” regulatory mode.

To validate this hypothesis, pairs of spatially adjacent cardiac cells (< 100-µm) were selected. Mechanical stimulation was applied to one quiescent cell (activation cell) using the mechanical probe (Fig. 3a-b). Notably, the probe did not physically interact with the target cell, eliminating direct mechanical interference. Upon mechanical stimulation of the activation cell (at 1.37 s), the adjacent target cell exhibited a rapid response (< 0.1 s delay), achieving full activation (Fig. 3c-d). This near-instantaneous activation of synchronization underscores efficient signal transmission through intercellular junctions. Both oscillatory and contractile responses in the activation cell successfully propagated to the target cell (Supplementary Video S2 and S3). Notably, the target cell maintained stable beating activation, while the activation cell gradually died due to mechanical stress, highlighting the non-destructive advantage of this regulatory mode. In 21 sets of experiments, 16 target cells were activated indirectly, and 5 were not activated (23.8%). Statistical analysis revealed a significant activation rate (76.2%, 16/21 cells, χ^2 test, $P < 0.05$, Fig. 3e), indicating that mechanical stimulation significantly activates target cells indirectly.

Furthermore, complementary experiments confirmed that signal transmission requires intact cell junctions: Spatially adjacent but uncoupled cell pairs failed to propagate activation (Figure S4, Supplementary Video S7 and S8), and cut cell junctions between coupled cells abolished synchronization (Figure S5, Supplementary Video S9). Calcium imaging (Sect. 3.3) further revealed that mechanical stimulation induces calcium influx in the activation cell, which propagates to the target cell via junctional pathways. This mechano-electric feedback mechanism transforms the activation cell into a transient “bioelectrical source”, enabling targeted regulation of adjacent cells.

This “cell activates cell” mode reproduces natural cardiac coordination in vitro while avoiding the shortcoming of traditional stimulation methods (e.g., diffuse electrical fields). The mechanical stimulation, combined with bioelectrical coupling, provides a non-destructive strategy to study and regulate intercellular communication. By applying mechanical stimulation and inherent cell-cell communication, we established a novel regulatory mode where a single activated cell serves as a cell activation button to regulate adjacent cells. This approach offers a framework for investigating arrhythmogenic mechanisms rooted in abnormal intercellular coupling.

Calcium imaging reveals the bioelectrical signal conduction mechanism of the “cell activates cell” mode under mechanical stimulation

Calcium ions, as an important second messenger in cells, whose change in concentration is often closely related to the excitation state of the cell and can characterize

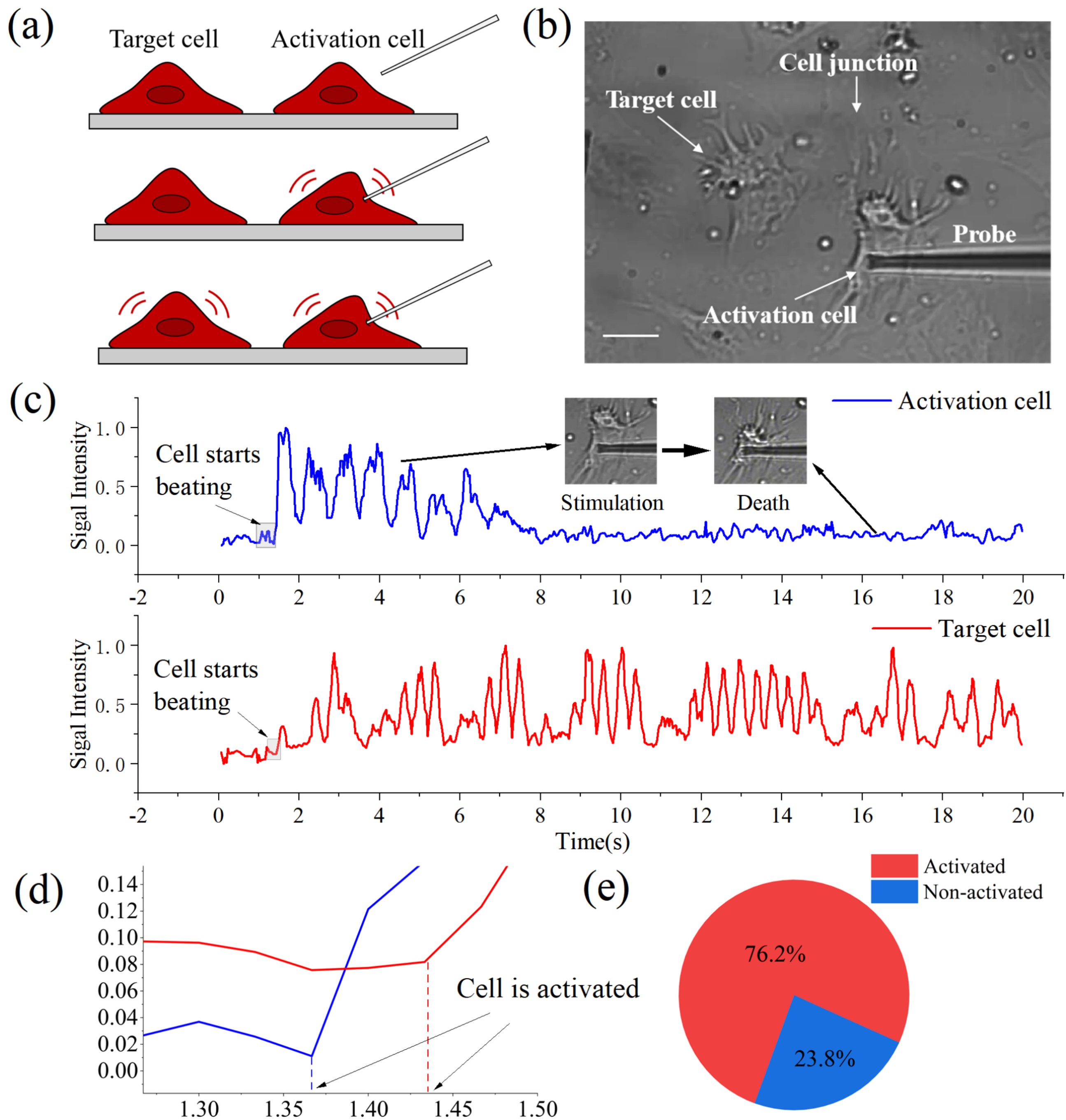


Fig. 3 Mechanically activated cardiac cell can act as "cell activation button" to activate adjacent cell. (**a**) and (**b**) show the schematic diagram and optical experimental image of the "cell activates cell" mode under mechanical stimulation. (**c**) Response curves of the activation cell(blue) and the target cell(red). (**d**) The activation cell is mechanically stimulated at 1.37 s, activating the target cell within < 0.1 s. (**e**) Percentage distribution of activated target cells($n = 21$ cells; 16 activated, 5 non-activated). Chi-square test confirms statistical significance ($*P < 0.05$). Scale bar: 30-μm

the electrophysiological activity of cardiac cells [19–21]. To explain the signaling mechanism underlying the "cell activates cell" mode, we utilized the Fluo-4 calcium ion fluorescent probe to monitor real-time calcium dynamics in activation cells and target cells during mechanical stimulation. Firstly, baseline calcium activity in unstimulated cardiac cells was characterized. As shown in Fig. 4a-b, spontaneously active cells exhibited a hierarchical calcium release pattern, with a "dominant cell" initiating sequential calcium transients in adjacent cells (Supplementary Video S4). This intrinsic behavior mirrors the natural pacemaker observed in cardiac syncytia, suggesting preexisting bioelectrical coupling among cultured cells.

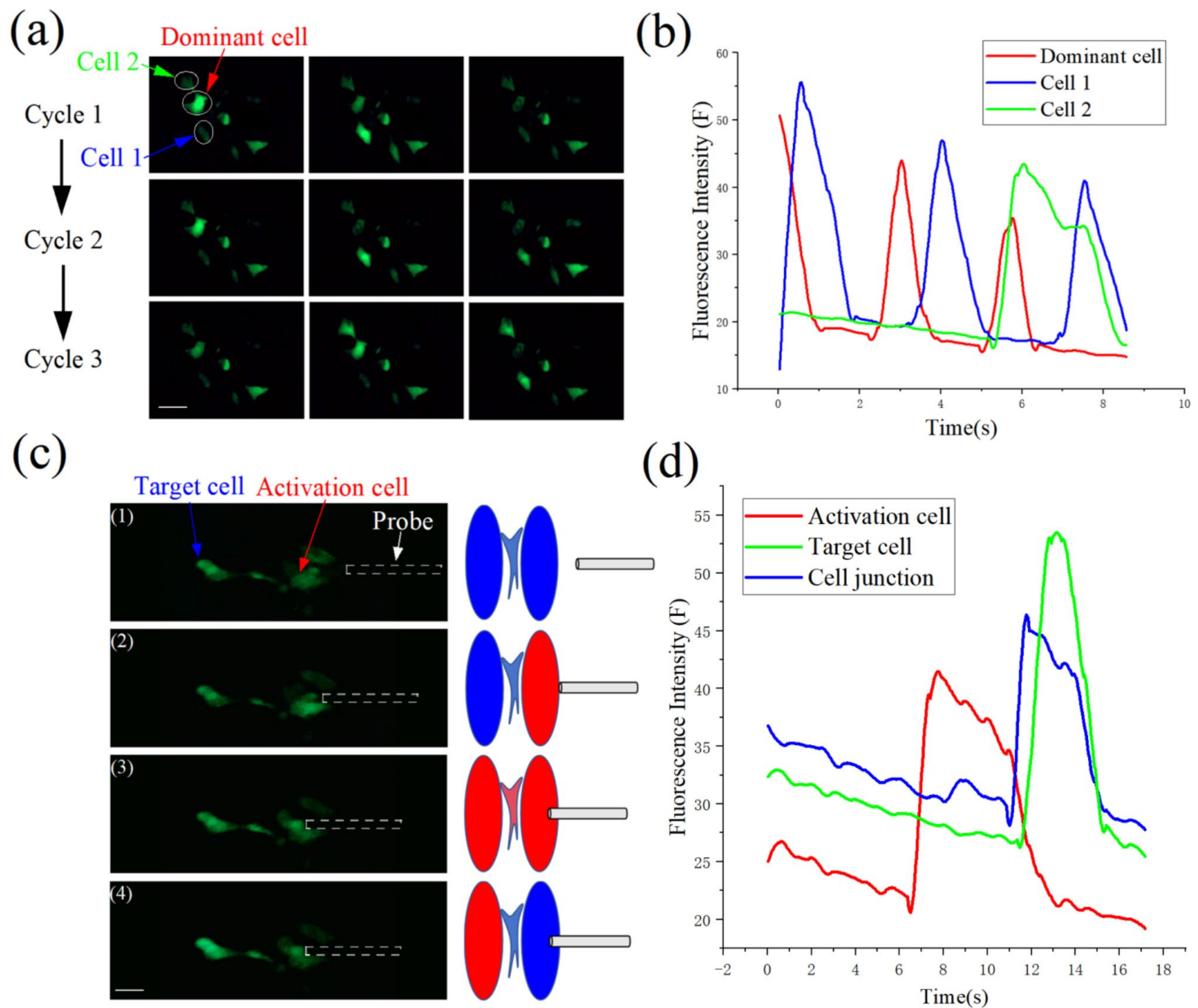


Fig. 4 Calcium imaging reveals the bioelectrical signal conduction mechanism. (**a-b**) Spontaneous calcium transients in unstimulated cells, showing hierarchical signaling from a "dominant cell" to adjacent cells. (**c-d**) Mechanical stimulation induces calcium influx in the activation cell, which propagates to the target cell via intercellular junctions. Scale bar: 30-μm

To verify whether mechanical stimulation could artificially establish such dominance, we selected pairs of adjacent cells with minimal baseline calcium activity (Fig. 4c,d). Upon local mechanical stimulation of the activation cell, rapid calcium influx occurred within the activated cell (Fig. 4c,d, 10–12 s). This response propagated to the target cell via cell junctions, inducing synchronized calcium transients with negligible delay (< 0.1 s; Fig. 4d, Supplementary Video S5). Notably, calcium propagation was spatially restricted to mechanically stimulated cell pairs, confirming signal specificity. The mechano-electrical transduction process exhibited two phases, firstly, initial calcium influx in the activation cell, likely mediated by mechanosensitive ion channels activated by membrane deformation. Secondly, Intercellular propagation via cell junctions, enabling rapid diffusion of calcium and depolarizing currents to the target cell. These findings align with the observed synchronization in Sect. 3.2 and provide direct evidence that mechanical stimulation enhances bioelectrical communication.

The temporal-spatial correlation between mechanical stimulation, calcium dynamics, and target cell activation underscores a causal chain: mechanical force to calcium-mediated excitation to intercellular electrical coupling. This mechanism effectively transforms quiescent cells into transient "bioelectrical sources", reproducing the hierarchical signaling observed in native cardiac tissue. By combining mechanical intervention with inherent cellular communication pathways, our approach offers a targeted strategy to regulate target cardiac cell networks without disrupting their microenvironment.

Discussion

This study presents a novel regulatory mode of "cell activates cell", providing a unique perspective on cardiac cell beating regulation. The following discussion unfolds from three aspects, namely the mechanistic basis, the impact of mechanical stimulation parameters, the limitations, and future directions, in combination with the research results.

Mechanistic basis of the "cell activates cell" mode

The ability of the mechanical probe to induce excitability in quiescent cells highlights its specificity and precision compared to traditional stimulation methods. Calcium imaging revealed that mechanically activated cells mimic "dominant cells", rapidly releasing calcium ions and propagating bioelectrical signals to adjacent cells. This process relies critically on intercellular communication pathways. Supplementary experiments confirmed that intact cell junctions are essential for signal transmission. Gap junctions, in particular, likely mediate electrical coupling, enabling rapid (< 0.1 s) signal propagation. Furthermore, mechanosensitive ion channels and calcium dynamics synergistically amplify mechanical stimulation into electrical responses, underscoring the mechano-electric feedback intrinsic to cardiac cells.

Impact of mechanical stimulation parameters

The phenotype of cell responses (oscillatory, contractile, or non-responding) depends on multiple factors, including mechanical sensitivity, intercellular coupling strength, and physiological state. The magnitude of mechanical deformation is a key factor determining the type of response. Smaller mechanical deformations (5–20%) typically induced rhythmic beating, while larger deformations led to transient contractions or cell damage. Given the flexibility of the system and method, the parameters of probe significantly influenced outcomes, finer probes (1-μm) risked membrane puncture and calcium overload, whereas coarser probes (20-μm) caused cell detachment. Stimulation angle, stimulation speed, and stimulation duration also influenced response outcomes immediately. These observations emphasize the need to optimize probe diameter, stimulation angle, stimulation speed, and duration to balance cell activation efficiency and cell viability.

Limitations and future directions

While our 2D culture system provided experimental simplicity and controllability, it lacks the 3D extracellular matrix interactions of native myocardium, which regulate cell polarity, mechano-sensing, and intercellular coupling [22–24]. Future studies should employ 3D models (e.g., engineered heart tissues, cardiac organoids) to better replicate physiological conditions.

Additionally, a quantitative framework linking stimulation intensity to response types is needed. Preliminary data suggest mechanical force alters response phenotypes nonlinearly: exceeding physiological thresholds compromises viability, while subthreshold forces fail to activate cells. Systematically exploring these relationships can provide directions for future research optimization, such as applications in the study of arrhythmia mechanisms or cardiac tissue engineering.

Conclusion

By integrating mechanical stimulation with natural intercellular communication, this study advances an innovative and non-damaging strategy for target cardiac cell regulation, demonstrating how a mechanical probe can transform a cardiac cell into a "cell activation button" to achieve the activation of adjacent target cell. This approach provides a novel perspective on the regulation of cardiac cell beating, deepening our understanding of mechano-electric feedback and the role of mechanical stimulation in enhancing intercellular electrical signaling. These findings are of great significance for understanding arrhythmia diseases caused by abnormal cell-cell communication.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12951-025-03244-x.

Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
Supplementary Material 4
Supplementary Material 5
Supplementary Material 6
Supplementary Material 7
Supplementary Material 8
Supplementary Material 9
Supplementary Material 10

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Author contributions
Z.C. conceived and conducted most of the experiments, contributing to the writing of the manuscript. Y.Z. (Y.J. Zhang) developed the micro manipulation platform for mechanical stimulation of cardiac cells. Y.Z. (Y.D. Zhang) and H.C. participated in the cell experiments mentioned in this study and provided valuable suggestions during the research process. D.Z. and Q.H. assisted in data collection and processing. Z.W. and M.S. participated in the discussion of research results and helped improving the manuscript. X.Z. and Y.L. conceptualized the overall research framework, coordinated research activities among team members, and were responsible for the final review and editing of the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All experiments in the present study were conducted in accordance with the Regulations on the Administration of Laboratory Animals (Ministry of Science and Technology of China). All procedures in the present study were approved by the Laboratory Animal Center Ethics Committee of Nankai University, Tianjin, China (approval number SYXK(Tianjin)2024-0013).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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