

# A magneto-responsive nanomesh biosensor for simultaneous mechanical stimulation and electrochemical detection

Received: 7 March 2025

Accepted: 18 August 2025

Published online: 02 September 2025

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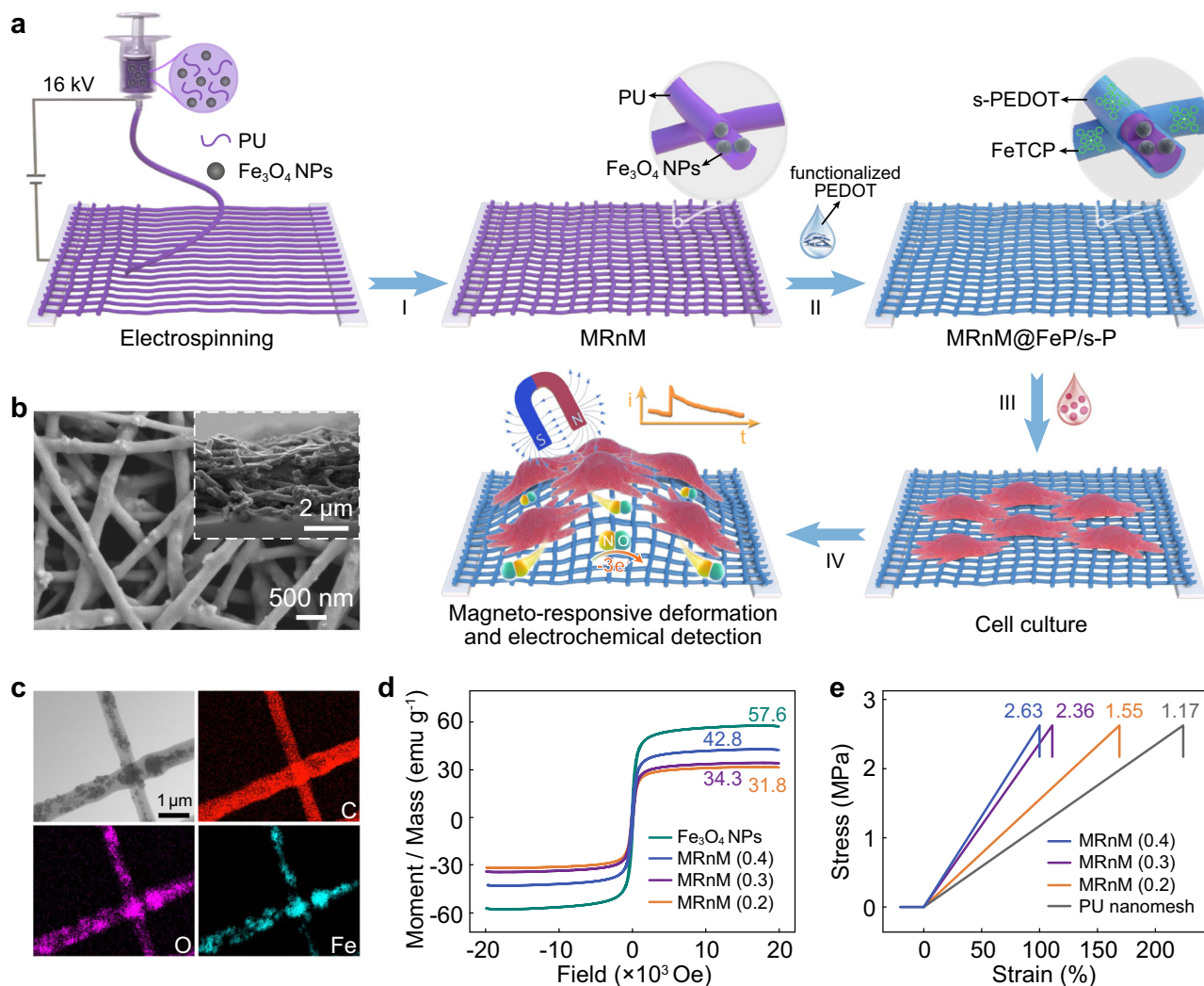
Mechanical cues are critical regulators of cell fate and behavior through the orchestrated and continual conversion of physical forces into biochemical responses. However, due to the poor compatibility between mechanical and biochemical techniques, existing methods are often limited in characterizing the occurring biochemical signals during mechanical stimulation. Herein, this work presents a magneto-responsive nanomesh (MRnM) biosensor capable of mechanically stimulating cells in vitro and tissues in vivo and simultaneously detecting the triggered biomolecules. Under external magnetic fields, the sensor exhibits excellent magnetic responsiveness with remote, controllable and tailored deformation, while maintaining prominent and stable electrochemical sensing performance. As a proof of concept, this MRnM sensor achieves the magnetically-actuated deformation of osteoblasts and real-time monitoring of the ensuing nitric oxide release, revealing the role of Piezo1 channels in nitric oxide synthase signaling pathways. Furthermore, we demonstrate the capability of MRnM sensor for in vivo applications. Ultimately, the developed MRnM biosensor holds great potential for mechanical stimulation and real-time monitoring of various biological systems, ranging from living cells to soft tissues and in vivo organs.

Cells and tissues within all living organisms experience mechanical forces and convert them into biochemical responses via cellular mechanotransduction, which plays a critical role in regulating cell metabolism, cell-cell signaling, tissue function and disease occurrence, such as osteoarthritis, atherosclerosis, neural degeneration and tumorigenesis<sup>1–3</sup>. The fundamental roles of mechanical stimuli on biological systems have become the cutting-edge research across numerous fields, for example, the newly emerging field of mechanobiology<sup>4,5</sup>. To understand how cells sense and respond to mechanical cues from the environment, substantial effort has been invested in developing biophysical techniques to reproduce and measure the forces applied to cells<sup>6</sup>, such as traction force microscopy<sup>7</sup>, atomic force microscopy<sup>8</sup>, magnetic and optical tweezer systems<sup>9,10</sup>, and molecular tension microscopy<sup>11</sup>. The ensuing

alteration in biochemical signals mostly rely on end point assays, including protein immunoassay<sup>12</sup>, genetic sequencing<sup>13</sup> and mass spectrometry<sup>14</sup>, due to the poor compatibility between mechanical loading and biochemical characterization techniques. Nonetheless, the conversion of mechanical stimuli into biochemical signals can be triggered rapidly (within a second) during mechanotransduction<sup>15</sup>, and understanding the early signaling events still lacks techniques that can simultaneously apply mechanical stimulation and monitor the evoked biochemical response.

As an important chemical analysis technique, electrochemical sensing has been widely employed in various healthcare, environmental, biomedical and food safety applications<sup>16–20</sup>, owing to the high sensitivity, fast response and low-cost instruments. The past decade has witnessed an exponential advancement in flexible

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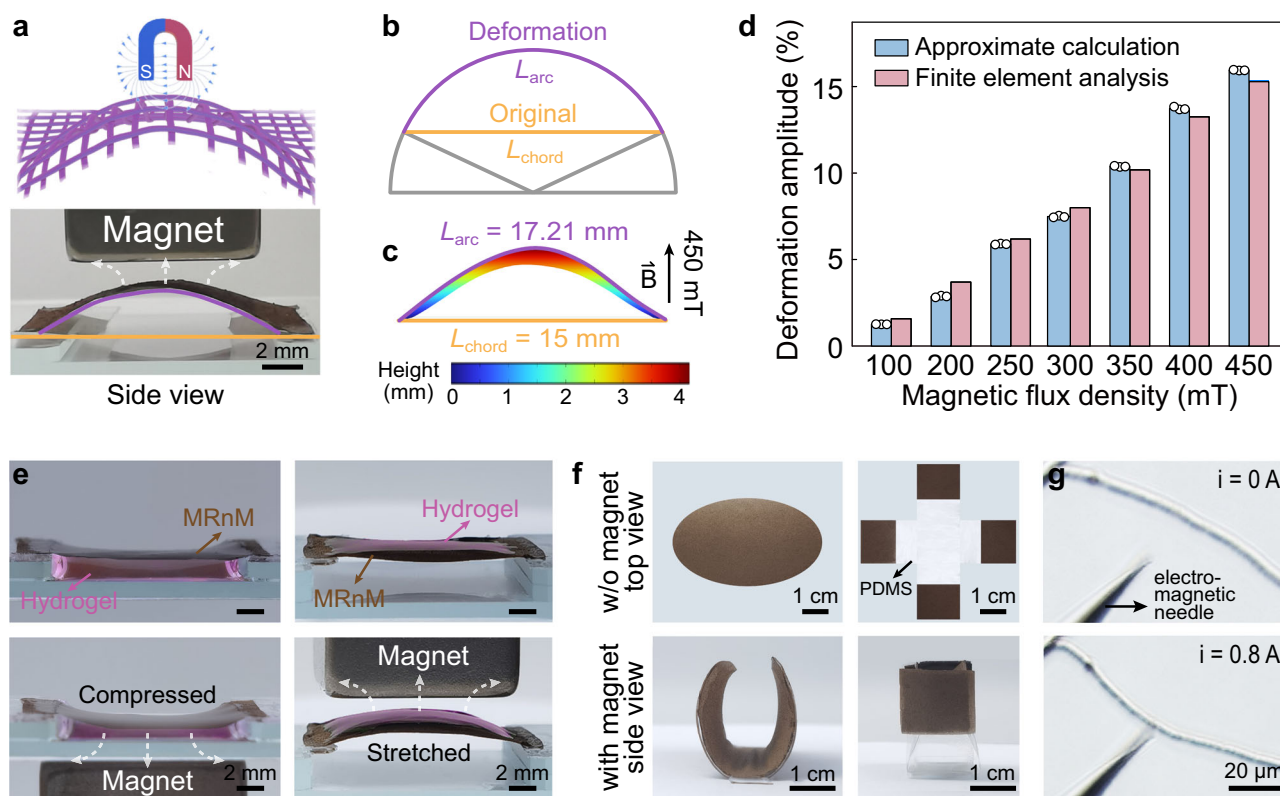
**Fig. 1 | The design principle and characterization of MRnM sensor. a** Schematic diagram for the MRnM sensor fabrication and electrochemical detection of mechanically-evoked biomolecules released from cells. **b** SEM images of MRnM.

Inset: the cross-section of MRnM. **c** TEM image of PU/Fe<sub>3</sub>O<sub>4</sub> nanofibers and corresponding EDX elemental mapping images (Fe<sub>3</sub>O<sub>4</sub> content: 0.4 g mL<sup>-1</sup>). **d** Magnetic hysteresis loops and **(e)** stress-strain curves of Fe<sub>3</sub>O<sub>4</sub> NPs and different MRnMs.

electronics, which also brings revolutionary changes to electrochemical sensors in diverse biological applications. The emergence of wearable electrochemical sensors allows noninvasive and continuous monitoring of biomarkers in biofluids<sup>21–23</sup>. Moreover, soft electrochemical sensors have achieved the measurement of ions and molecules in vivo<sup>24–28</sup>, ranging from Ca<sup>2+</sup> and glucose in the venous blood, nitric oxide (NO) in the articular cavity, biochemicals (lactate, glucose, NO and H<sup>+</sup>) in amniotic fluid, and neurotransmitters (dopamine and serotonin) in the brain and gut. In the context of cell detection, soft sensors have provided a novel research paradigm for exploring the still unclear mechanotransduction pathway by real-time monitoring of mechanically stretch-evoked molecules from cells<sup>29,30</sup>, such as NO and H<sub>2</sub>O<sub>2</sub> molecules from endothelial cells and chondrocytes<sup>31–34</sup>, and dopamine and serotonin release from endocrine cells<sup>35,36</sup>. Despite these exciting advances, existing sensors are only capable of complying with the deformation of soft cells and tissues, and still require the aid of rigid and bulky systems (e.g., stepper motor) to load mechanical stimulation to cells. This heavily hinders the active and controllable manipulation of living cells in vitro, and the reliance on peripheral devices also impedes the mechanical modulation and electrochemical detection of tissues in vivo. Therefore, a

controllable and remotely actuated electrochemical biosensor remains highly attractive and has yet to be realized.

To bridge this gap, we have engineered a magneto-responsive nanomesh (MRnM) biosensor for simultaneous mechanical stimulation and electrochemical monitoring of biological systems (Fig. 1a). This sensor was fabricated by electrospinning a solution of polyurethane (PU) and Fe<sub>3</sub>O<sub>4</sub> nanoparticles (Fe<sub>3</sub>O<sub>4</sub> NPs) to form a self-supporting PU/Fe<sub>3</sub>O<sub>4</sub> nanomesh. The Young's modulus (2.63 MPa) of PU/Fe<sub>3</sub>O<sub>4</sub> nanomesh is much lower than that of typically used flexible films (e.g., polyimide and polyethylene terephthalate, higher than 1 GPa)<sup>37,38</sup>. Notably, the nanomesh exhibited strong magnetic responsiveness, enabling remote, controllable and tailored deformation. Subsequently, a tunable conductive polymer was assembled onto the surface of MRnM to ensure prominent and stable electrochemical sensing performance. When an external magnetic field was applied, the MRnM sensor with cells cultured thereon could undergo mechanical deformation and monitor the mechanically-evoked biomolecules released from cells in situ. In this proof-of-concept study, we explored the real-time release of NO molecules from MC3T3-E1 cells (a widely used cell line of pre-osteoblasts) triggered by magnetically-actuated deformation, as well as mechanical manipulation and electrochemical monitoring of tissues in vivo.



**Fig. 2 | Magneto-responsive deformation of MRnM.** **a** Schematic illustration (top) and digital image (bottom) of the magneto-responsive deformed MRnM. **b** Approximate calculation model, **c** FEA model and **(d)** corresponding deformation amplitude of the MRnM under different magnetic field intensity. Data are presented

as mean  $\pm$  s.e.m. ( $n = 3$ , for each group). **e** Digital images of the magneto-responsive deformed MRnM and hydrogel. **f** Tailored deformation of MRnM. **g** Local deformation of a single PU/Fe<sub>3</sub>O<sub>4</sub> nanofiber actuated by an electromagnetic needle.

## Results

### Fabrication of MRnM

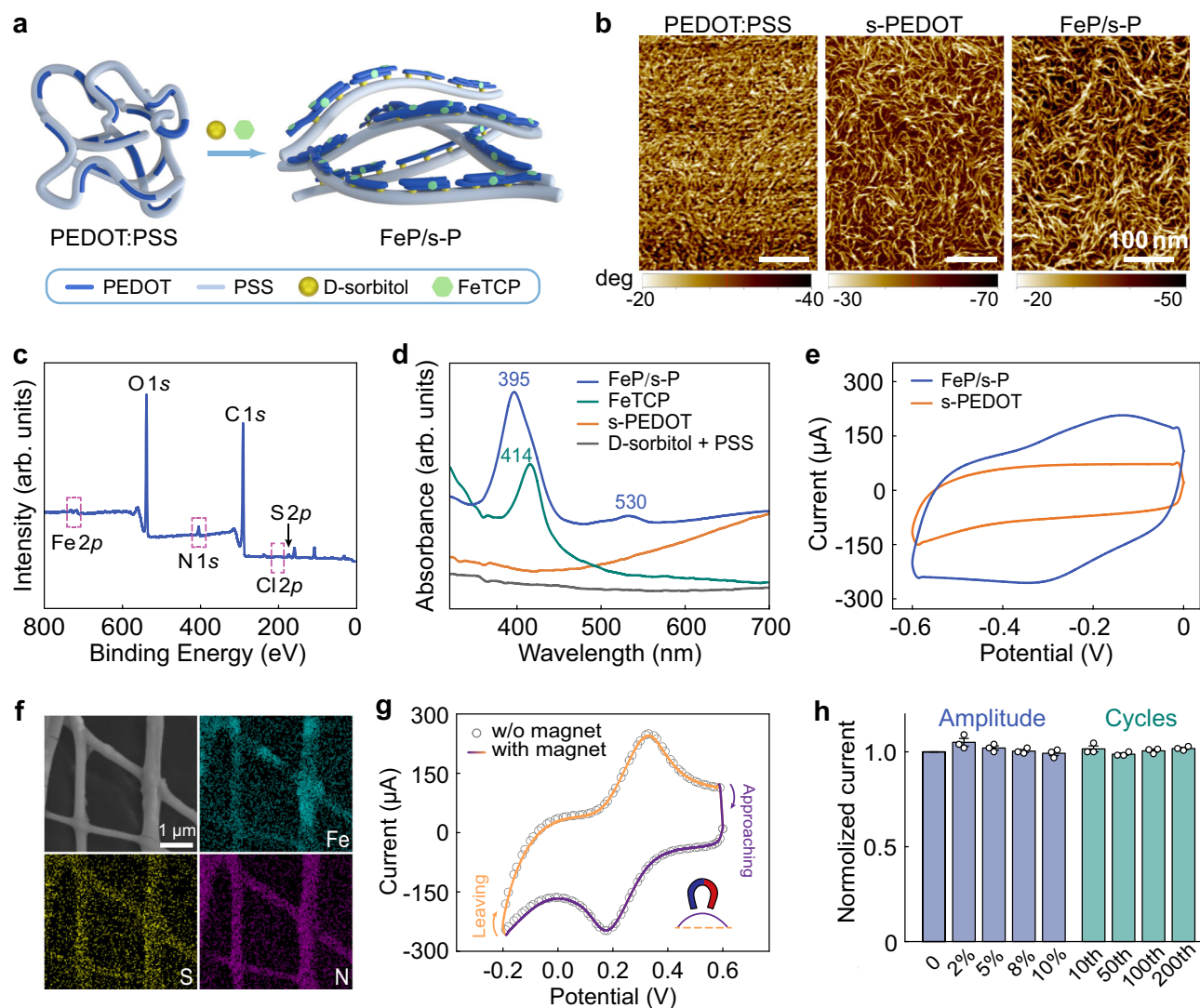
The MRnM was fabricated via electrospinning a homogeneous suspension containing PU, Fe<sub>3</sub>O<sub>4</sub> NPs (20–30 nm), N,N-dimethylformamide (DMF) and tetrahydrofuran (THF) onto a polydimethylsiloxane (PDMS) frame (Fig. 1a and Supplementary Fig. 1). Scanning electron microscopy (SEM) images showed a uniform and continuous distribution of PU/Fe<sub>3</sub>O<sub>4</sub> nanofibers with diameters ranging from 300 to 400 nm, and the thickness of nanofibers-based nanomesh was approximately 4  $\mu$ m (Fig. 1b). Since the Fe<sub>3</sub>O<sub>4</sub> NPs content in PU/Fe<sub>3</sub>O<sub>4</sub> nanofibers directly affects the magnetic responsiveness and mechanical property of stretchable electrodes, nanofibers with varying Fe<sub>3</sub>O<sub>4</sub> NPs contents (0.2, 0.3, 0.4 and 0.5 g mL<sup>-1</sup>) in electrospinning solutions were initially prepared. While a 0.5 g mL<sup>-1</sup> concentration of Fe<sub>3</sub>O<sub>4</sub> NPs significantly increased the viscosity of the solution, leading to frequent nozzle clogging during the electrospinning process. Consequently, 0.4 g mL<sup>-1</sup> Fe<sub>3</sub>O<sub>4</sub> NPs was chosen as the maximum concentration. Transmission electron microscopy (TEM) images showed an increased amount of Fe<sub>3</sub>O<sub>4</sub> NPs encapsulated within the nanofibers as the Fe<sub>3</sub>O<sub>4</sub> NPs concentration increased (Supplementary Fig. 2). Even when the concentration was high as 0.4 g mL<sup>-1</sup>, Fe<sub>3</sub>O<sub>4</sub> NPs could still uniformly distribute in PU nanofibers, with little effect on the diameter of the electrospun nanofibers (Supplementary Fig. 3). Energy-dispersive X-ray (EDX) mapping confirmed the presence of Fe element from Fe<sub>3</sub>O<sub>4</sub> NPs and C element from PU, further demonstrating the dense and uniform distribution of Fe<sub>3</sub>O<sub>4</sub> NPs in PU nanofibers (Fig. 1c).

The magnetic and mechanical properties of different MRnMs were characterized by magnetic hysteresis loops and stress-strain curves. All magnetic hysteresis loops intersected the origin, indicating the negligible remanence and coercivity in the absence of an external magnetic field (Fig. 1d). The maximum magnetization value increased

with the Fe<sub>3</sub>O<sub>4</sub> NPs concentration in electrospinning solutions, and reached up to 42.8 emu g<sup>-1</sup> for MRnM with 0.4 g mL<sup>-1</sup> Fe<sub>3</sub>O<sub>4</sub> NPs. Tensile test showed that the Young's modulus of these self-supporting nanomeshes ranged from  $1.17 \pm 0.02$  to  $2.63 \pm 0.25$  MPa (Fig. 1e), which is close to the stiffness of many natural extracellular matrices, such as dermal and osteoid tissues<sup>39</sup>. Thus, 0.4 g mL<sup>-1</sup> Fe<sub>3</sub>O<sub>4</sub> NPs was added into the ultimate electrospinning solution to obtain MRnMs with rapid magnetic responsiveness.

### Magneto-responsive deformation of MRnM

The magnetic responsiveness of MRnM was investigated by positioning a NdFeB permanent magnet directly above a rectangular nanomesh with the two ends fixed. As the magnet approached, MRnM underwent rapid deformations along the direction of the magnetic field (Fig. 2a and Movie S1). Herein, considering the shape change from a straight line (Fig. 2a, orange curve) to a similar arc (Fig. 2a, purple curve) when viewed from the side, the deformation of the MRnM could be approximated as stretching the chord of a specific circle to overlap with the corresponding arc (Fig. 2b and Supplementary Fig. 4). In this case, the deformation amplitude was calculated as the ratio of the increased length to the original chord length, that was  $(L_{\text{arc}} - L_{\text{chord}})/L_{\text{chord}}$ . To validate this approximation, finite element analysis (FEA) was further performed to quantify the deformation amplitude of the nanomesh (Fig. 2c and Supplementary Figs. 5, 6). With magnetic field intensity ranging from 100 mT to 450 mT, the results of approximate calculation and FEA exhibited good consistency (Fig. 2d and Supplementary Figs. 7, 8). Furthermore, FEA results demonstrated that the stress on the MRnM surface increased with the magnetic field strength (Supplementary Fig. 9), indicating that the stress distribution could be effectively controlled by the external magnet.



**Fig. 3 | FeP/s-P characterization and assembly on MRnM.** **a** Schematic illustration showing the microstructures of pristine PEDOT:PSS and FeP/s-P. **b** AFM phase images of different PEDOT-based films. **c** The full XPS spectrum of FeP/s-P. **d** UV-visible spectra of different solutions. **e** CV curves of s-PEDOT and FeP/s-P based films in 0.1 M PBS. Scan rate: 50 mV s<sup>-1</sup>. **f** SEM image and corresponding EDX elemental mapping images of MRnM@FeP/s-P. **g** CV curves of MRnM@FeP/s-P sensor

during the magneto-responsive deformation process. Scan rate: 50 mV s<sup>-1</sup>. **h** The normalized oxidation peak currents of CV curves recorded by MRnM@FeP/s-P sensor obtained in 1 mM K<sub>3</sub>[Fe(CN)<sub>6</sub>] after being deformed with different amplitudes and 10% deformation for different cycles. Data are presented as mean ± s.e.m. (n = 3, for each group).

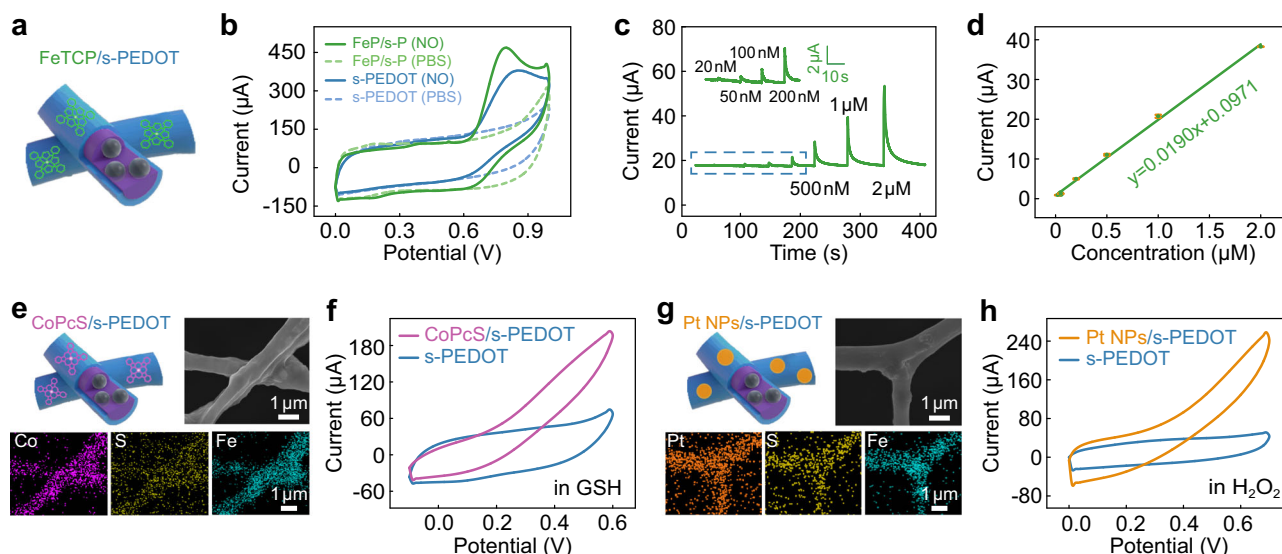
The magnetic responsiveness of MRnM provided numerous opportunities for multiform mechanical manipulation and deformation. For example, placing a hydrogel slice either below or above the MRnM enabled straightforward compression and stretching of the hydrogel (Fig. 2e). When the MRnM was attached to an elastic substrate, magnetic manipulation allowed the PDMS film to be shaped into various configurations, ranging from the simple bending of a 2D elliptical PDMS to the complex 3D confluence of a patterned PDMS sheet (Fig. 2f and Movie S2). Beyond the overall deformation, local and precise manipulation of a single nanofiber could be achieved using an electromagnetic needle tip as a focused magnetic field hotspot (Fig. 2g and Movie S3), a feat that remains notably challenging for most reported magnetic actuators. Collectively, the MRnM exhibited excellent magnetic responsiveness, enabling remote, controllable and tailored deformations.

### FeP/s-P preparation and assembly on MRnM

To achieve simultaneous mechanical manipulation and electrochemical detection, the MRnM required further assembly with sensing

materials that possess high stretchability and sensitivity to ensure stable and accurate measurements during the magneto-responsive deformation process. Conductive polymer poly(3,4-ethylenedioxythiophene) (PEDOT) has emerged as an excellent candidate due to its ease of processing, superior conductivity and electrochemical performance<sup>40,41</sup>. However, commercial PEDOT is usually dispersed in poly(styrene sulfonate) (PSS) solution to address its insolubility<sup>42</sup>, which results in reduced conductivity and lower fracture strain of PEDOT:PSS film. In light of advancements in PEDOT-based materials<sup>43,44</sup>, biocompatible D-sorbitol has been selected as a perfect dopant to improve the conductivity and stretchability<sup>45</sup>. Additionally, in view of the excellent electrocatalytic property of Fe(III) meso-tetra (4-carboxyphenyl) porphyrin (FeTCP) toward NO oxidation<sup>46</sup>, FeTCP was co-incorporated into PEDOT:PSS solution to enhance the NO sensing capability (Fig. 3a).

Atomic force microscope (AFM) images showed that PEDOT:PSS appeared as very tiny grains, while D-sorbitol doped PEDOT:PSS (s-PEDOT) displayed interconnected nanofibrous structures with notable continuity (Fig. 3b). These morphological changes were attributed to



**Fig. 4 | Characterization of functionalized PEDOT-based MRnM sensors.**

**a** Schematic illustration of MRnM@FeP/s-P sensor. **b** CV curves of MRnM@FeP/s-P and MRnM@s-PEDOT sensors obtained in PBS with or without 50  $\mu\text{M}$  NO. **c** Amperometric responses and **(d)** calibration curve of MRnM@FeP/s-P sensor to NO at a potential of + 0.80 V (vs. Ag/AgCl). Data are presented as mean  $\pm$  s.e.m. ( $n = 3$ , for each group). Inset: the enlargements of amperometric responses framed

in blue. **e** Schematic illustration and SEM image of MRnM@CoPcS/s-PEDOT and EDX elemental mapping images. **f** CV curves of MRnM@CoPcS/s-PEDOT and MRnM@s-PEDOT sensors obtained in PBS with 100 mM GSH. **g** Schematic illustration and SEM image of MRnM@Pt NPs/s-PEDOT and EDX elemental mapping images. **h** CV curves of MRnM@Pt NPs/s-PEDOT and MRnM@s-PEDOT sensors obtained in PBS with 1 mM  $\text{H}_2\text{O}_2$ . Scan rate: 50  $\text{mV s}^{-1}$ .

the fact that D-sorbitol could weaken the interaction between PEDOT and PSS and promote phase separation (Supplementary Fig. 10)<sup>45</sup>, resulting in the PEDOT-enriched region for enhanced conductivity, stretchability and electrochemical stability (Supplementary Figs. 11, 12)<sup>47</sup>. Notably, the incorporation of FeTCP into s-PEDOT (FeP/s-P) did not significantly alter the nanofiber morphology of s-PEDOT (Fig. 3b). The full X-ray photoelectron spectroscopy (XPS) spectrum of FeP/s-P, together with the deconvolution of S 2p, Cl 2p, C 1s, N 1s, O 1s and Fe 2p spectra, confirmed the presence of S, Cl, C, N, O and Fe elements (Fig. 3c and Supplementary Fig. 13), where S was associated with PEDOT, and Fe, Cl, N were corresponded to FeTCP. Compared with that of FeTCP, the UV/Vis spectrum of FeP/s-P showed the blue shift of Soret band of FeTCP from 414 nm to 395 nm, indicating the  $\pi$ - $\pi$  interactions between PEDOT and FeTCP (Fig. 3d). Cyclic voltammetry (CV) response of FeP/s-P electrode in phosphate-buffered saline (PBS) displayed a pair of redox peaks within the potential range of  $-0.6$  V to 0 V, which was attributed to the electron transfer process between Fe (II) and Fe (III) at the core of FeTCP (Fig. 3e)<sup>46</sup>. These results demonstrated the successful functionalization of PEDOT:PSS with the plasticizer D-sorbitol and the molecular catalyst FeTCP.

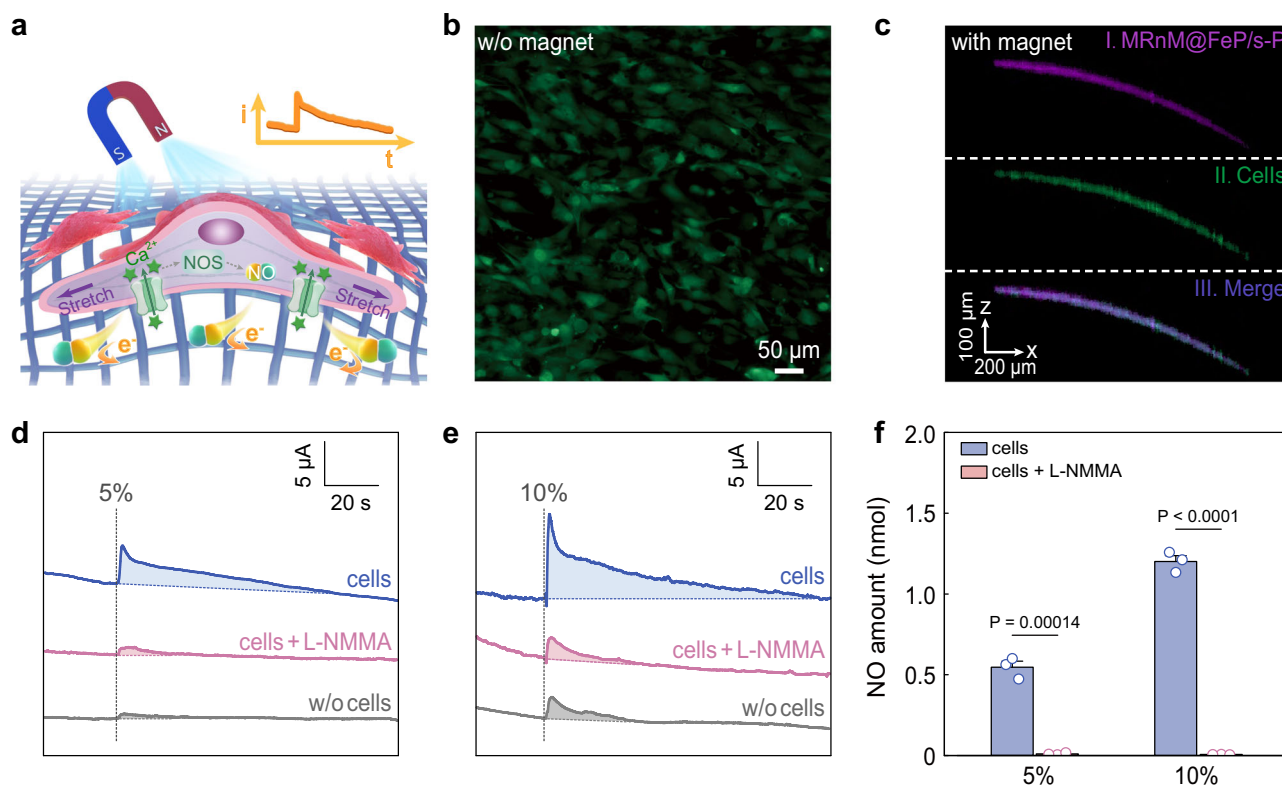
Subsequently, the MRnM was pretreated with plasma and immersed in FeP/s-P solution for 20 min to ensure the assembly of FeP/s-P on the surface of MRnM (Supplementary Fig. 14). SEM-EDX mapping results showed the clear co-localization of S and Fe elements along the skeleton of  $\text{PU/Fe}_3\text{O}_4$  nanofibers (Fig. 3f). Tensile test revealed that FeP/s-P coating increased the Young's modulus slightly, from 2.63 to 3.31 MPa, compared to the bare MRnM, while the maximum deformation amplitude of MRnM@FeP/s-P sensor could still reach 10% (Supplementary Fig. 15). To assess the electrical stability, the resistance of MRnM@FeP/s-P sensor was recorded when subjected to 0, 5% and 10% deformations, which showed no significant variation in resistance during deformation (Supplementary Fig. 16). Furthermore, the electrochemical stability of MRnM@FeP/s-P sensor was evaluated by recording CV response in  $\text{K}_3[\text{Fe}(\text{CN})_6]$  solution during the deformation process. When an external magnet was approaching to or leaving from the MRnM@FeP/s-P sensor for dynamic deformation, the recorded CV curve was perfectly consistent with that of the original

undeformed state (Fig. 3g). Even though the MRnM@FeP/s-P sensor was subjected to sequential magneto-responsive deformation with varying amplitudes (0–10%) or repeated 10% deformation for 200 cycles, there was little change in the oxidation peak currents, manifesting the prominent electrochemical stability (Fig. 3h and Supplementary Fig. 17). Altogether, these results demonstrated the uniform and robust assembly of FeP/s-P on the MRnM.

### Electrochemical sensing performance of functionalized PEDOT-based MRnMs

NO is an important endogenous messenger involved in various physiological processes, and aberrant NO signaling is strongly implicated in the pathogenesis of many organ disorders<sup>48–51</sup>. Therefore, quantitative monitoring of NO is crucial for understanding its diverse pathophysiological functions<sup>52</sup>. CV curves were recorded in PBS containing 50  $\mu\text{M}$  NO to evaluate the electrochemical sensing performance of the FeP/s-P coated on MRnM (Fig. 4a, b). Compared to that of s-PEDOT, the peak potential of NO oxidation on FeP/s-P shifted negatively from 0.85 V to 0.79 V with an elevated oxidation peak current. This shift was attributed to the fact that FeTCP (as an electronic mediator) could catalyze the oxidation of NO to  $\text{NO}_3^-$  via the redox reaction between Fe(II) and Fe(III). Notably, when an external magnetic field was applied, the MRnM@FeP/s-P maintained stable electrochemical sensing during the magneto-responsive deformation process (Supplementary Fig. 18). The superiority of FeP/s-P in NO electro-oxidation was further demonstrated by the amperometric responses to a series of NO solutions with increasing concentrations (Fig. 4c). The corresponding calibration curves displayed a good linear relationship with NO across a wide concentration range from 20 nM to 2  $\mu\text{M}$ , with a calculated detection limit of 5 nM ( $\text{S/N} = 3$ ) (Fig. 4d), manifesting the excellent electrochemical sensing ability of MRnM@FeP/s-P for NO detection.

In addition to FeTCP, the incorporation of other catalysts into the s-PEDOT solution could enable MRnM to detect a broader range of analytes. For example, sulfonated cobalt phthalocyanine (CoPcS), a biomimetic molecular catalyst with distinct catalytic activity to biothiols<sup>53</sup>, was dissolved in s-PEDOT solution and possibly



**Fig. 5 | Magneto-responsive deformation and electrochemical monitoring of osteoblasts.** **a** Schematic illustration of magneto-responsive deformation and electrochemical detection. **b** Fluorescence image of MC3T3-E1 cells stained with Calcein-AM (green) and PI (red) after being cultured on MRnM@FeP/s-P sensor for 36 h. **c** Side view of the confocal microscope images of MRnM@FeP/s-P (fuchsia) and MC3T3-E1 cells (green) under magneto-responsive deformation.

**d, e** Amperometric responses and **(f)** the corresponding quantitative analysis of NO molecules detected from MC3T3-E1 cells under different deformation amplitudes. The vertical gray dashed lines indicate the beginning of deformation. Applied potential: +0.80 V (vs. Ag/AgCl). Data are presented as mean  $\pm$  s.e.m.; two-tailed Student's t-test ( $n = 3$ , for each group).

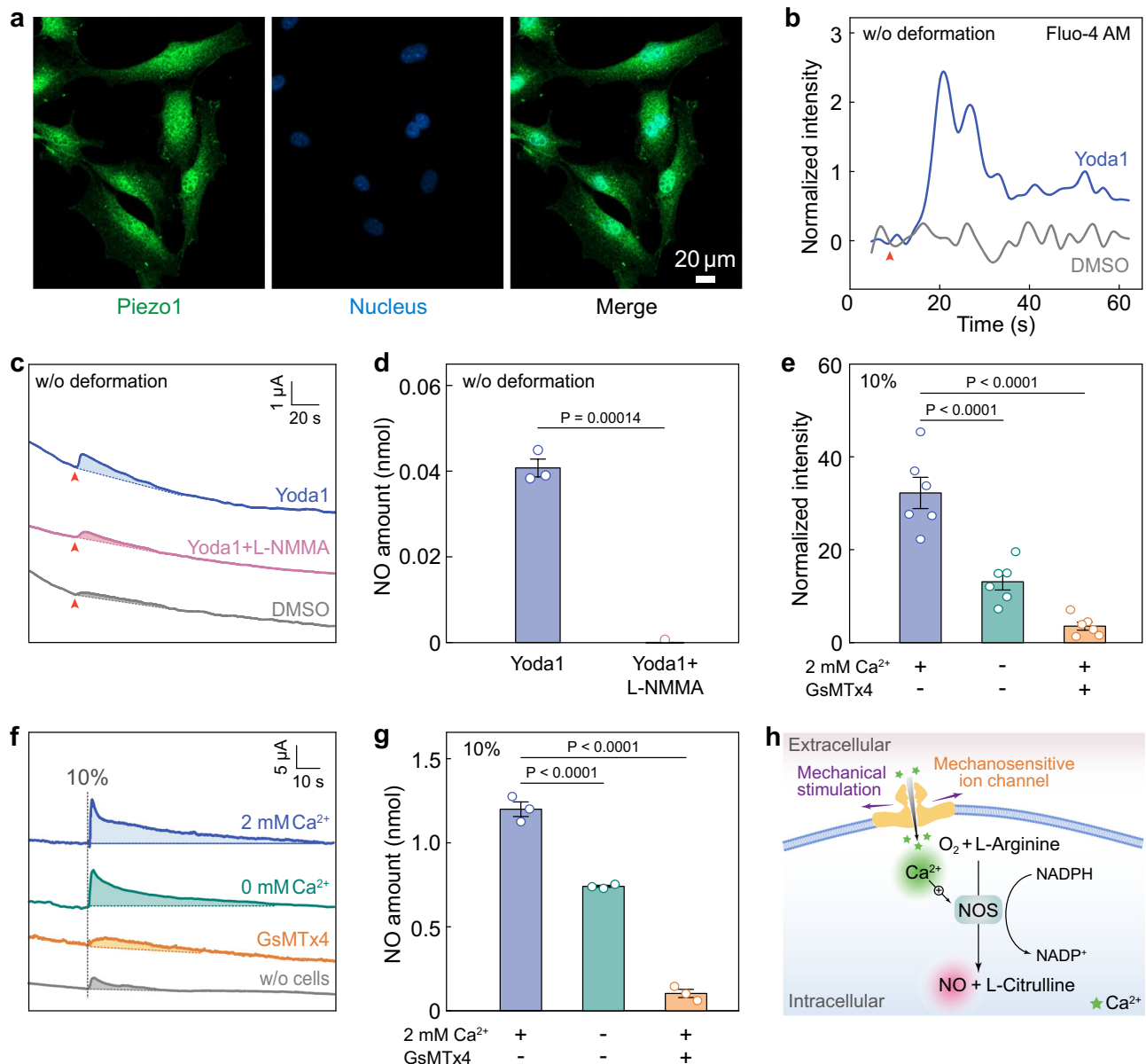
interacted with positively charged PEDOT via electrostatic interaction (Supplementary Fig. 19a). SEM-EDX mapping results showed that the characteristic Co element of CoPcS was uniformly distributed on the PU/Fe<sub>3</sub>O<sub>4</sub> nanofibers (Fig. 4e). CV curves of CoPcS/s-PEDOT coated MRnM (MRnM@CoPcS/s-PEDOT) sensor exhibited remarkable electrocatalytic performance for the glutathione (GSH) oxidation (Fig. 4f). Similarly, the addition of noble metal nanoparticles (NPs) into s-PEDOT solution provides an alternative approach to enhance the catalytic performance of MRnM sensor. For example, negatively charged Pt NPs were synthesized by reducing H<sub>2</sub>PtCl<sub>6</sub> with NaBH<sub>4</sub> and subsequently added to s-PEDOT solution (Supplementary Fig. 19b)<sup>54</sup>. The distribution of Pt element on the PU/Fe<sub>3</sub>O<sub>4</sub> nanofibers confirmed the successful modification with Pt NPs (Fig. 4g), and the MRnM@Pt NPs/s-PEDOT sensor exhibited significant catalytic activity for H<sub>2</sub>O<sub>2</sub> electrooxidation (Fig. 4h). This convenient and versatile strategy for coating functionalized and tunable PEDOT on MRnM could broaden the application of MRnM-based sensors in electrochemical detection.

### Magnetic manipulation and real-time monitoring of pre-osteoblasts

Bone is a highly dynamic tissue that adapts to mechanical stimuli by remodeling its mass and structure<sup>55,56</sup>. Although NO has long been recognized as an important signaling molecule in the mechanical adaptation of bone, real-time tracking of mechanically activated NO signaling in bone lineage cells has not yet been reported<sup>57,58</sup>. Among bone lineage cells, osteoblasts play a vital role in bone formation and remodeling, making them an ideal model for studying

mechanotransduction processes. Accordingly, MC3T3-E1 cells, a widely used cell line of pre-osteoblasts, were seeded onto the MRnM@FeP/s-P sensor for mechanical loading and electrochemical monitoring (Fig. 5a). MC3T3-E1 cells were stained with live/dead cell markers Calcein-AM and propidium iodide (PI) after being cultured on MRnM@FeP/s-P sensor for 36 h, and the fluorescence images showed that nearly all the cells exhibited high viability (Fig. 5b). Moreover, when an external magnetic field was applied to achieve 10% deformation (Movie S4), the side-view images of CellTracker-labeled cells and rhodamine-labeled MRnM@FeP/s-P sensor overlapped perfectly (Fig. 5c), indicating the firm adhesion of MC3T3-E1 cells to the underlying sensor during synchronous deformation.

As a proof of concept, 5% and 10% deformation amplitudes were applied to investigate the effect of mechanical stimulation on NO production from MC3T3-E1 cells (Fig. 5d, e and Supplementary Fig. 20). Upon the magnetic manipulation, the MRnM@FeP/s-P sensor recorded a rapid rise in the amperometric curve at the oxidation potential of NO, which subsequently returned to the baseline within 100 s. To verify that the elevated current was due to mechanically-evoked NO release, MC3T3-E1 cells were pretreated with L-NMMA to inhibit the activity of nitric oxide synthase (NOS)<sup>59</sup>, and the recorded current response was comparable to that of the MRnM@FeP/s-P sensor without cells thereon. Quantitative analysis was conducted by subtracting the current signals from mechanical disturbance in the amperometric curves to calculate the detected NO amounts, and the amounts of mechanically-evoked NO molecules were  $0.55 \pm 0.03$  nmol for 5% deformation and  $1.20 \pm 0.04$  nmol for 10% deformation (Fig. 5f). Note that the negligible impact of the external magnetic field on



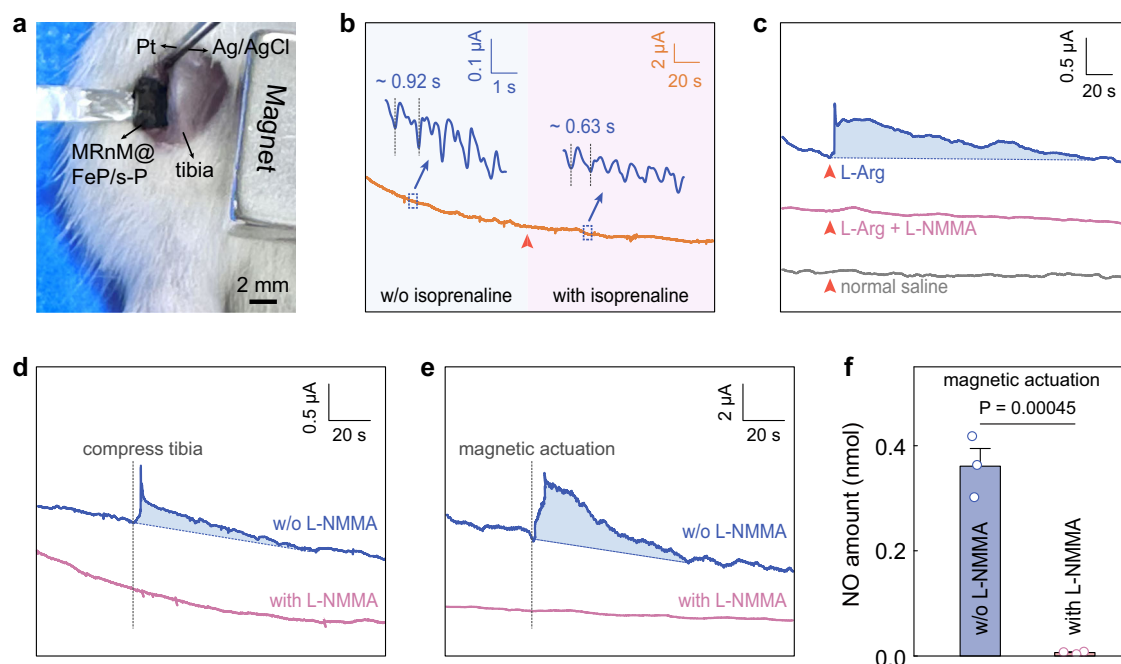
**Fig. 6 | Piezo1 channels-involved NO signaling pathways.** **a** Piezo1 (green) and nucleus (blue) immunofluorescence staining of MC3T3-E1 cells. **b** Normalized  $\text{Ca}^{2+}$  fluorescence intensity traces (relative to unstimulated cells) of MC3T3-E1 cells in response to the application of Yoda1 (40  $\mu$ M) and DMSO. **c** Amperometric responses and (d) the corresponding quantitative analysis of NO molecules detected from MC3T3-E1 cells stimulated by 40  $\mu$ M Yoda1. The red triangle indicates the reagent addition. Applied potential: +0.80 V (vs. Ag/AgCl). Data are presented as mean  $\pm$  s.e.m.; two-tailed Student's *t*-test ( $n = 3$ , for each group). **e** Normalized peak  $\text{Ca}^{2+}$

fluorescence intensity (relative to the undeformed cells) of MC3T3-E1 cells induced by 10% magneto-responsive deformation under different conditions. Data are presented as mean  $\pm$  s.e.m.; one-way ANOVA ( $n = 6$ , for each group). **f** Amperometric responses and (g) the corresponding quantitative analysis of NO molecules detected from MC3T3-E1 cells under different conditions. The vertical gray dashed line indicates the beginning of 10% deformation. Applied potential: +0.80 V (vs. Ag/AgCl). Data are presented as mean  $\pm$  s.e.m.; one-way ANOVA ( $n = 3$ , for each group). **h** Schematic diagram showing the mechanically activated NO signaling pathways.

electrochemical detection was confirmed by immobilizing the MRnM@FeP/s-P sensor on a glass slide to restrict its mechanical deformation (Supplementary Fig. 21).

Piezo1 is a mechanically activated cation channel and is expressed in various mechanosensory cells, including the bone lineage cells<sup>60–62</sup>. To investigate whether Piezo1 is involved in the mechanically-evoked NO release from MC3T3-E1 cells, immunofluorescence staining (Fig. 6a) and Western Blot analysis (Supplementary Fig. 22) of Piezo1 were conducted, which demonstrated the high expression of Piezo1 protein in MC3T3-E1 cells. Given that Piezo1 is a non-selective cation channel with a slight preference for  $\text{Ca}^{2+}$ , cells were treated with Piezo1-specific agonist Yoda1 (40  $\mu$ M), extracellular  $\text{Ca}^{2+}$  (2 mM) or GsMTx4

(10  $\mu$ M, a widely used inhibitor for cationic mechanosensitive channels) to further assess the function of Piezo1 protein<sup>63,64</sup>. Upon Yoda1 stimulation, both intracellular  $\text{Ca}^{2+}$  and NO responses were monitored in real time. The dynamic trace of intracellular  $\text{Ca}^{2+}$  fluorescence revealed a transient and robust increase following Yoda1 addition (Fig. 6b), indicating the participation of Piezo1 activation. Simultaneously, the MRnM@FeP/s-P sensor recorded a significantly higher current rise compared to control groups (DMSO solvent, Yoda1 + L-NMMA (NOS inhibitor), Fig. 6c). Quantitative analysis showed that Yoda1-induced NO release from the MC3T3-E1 cells was approximately 0.04 nmol (Fig. 6d), suggesting that Piezo1 activation (triggering  $\text{Ca}^{2+}$  entry) could result in the downstream NO generation in MC3T3-E1 cells.



**Fig. 7 | Electrochemical monitoring and magnetic manipulation in vivo.** **a** The photo of an electrochemical detection experiment in vivo. **b** Amperometric curves of the rat before and after isoprenaline injection. Inset: the enlargements of amperometric responses framed in blue. Amperometric responses detected from the mid-shaft of a rat's tibia with **(c)** chemical stimuli and **(d)** mechanical

compression at the distal end of the tibia. **e** Amperometric responses and **(f)** the corresponding quantitative analysis of NO amount from magnetically actuated tibia. The red triangles indicate the reagent addition. The vertical gray dashed lines indicate the beginning of stimulations. Applied potential: +0.80 V (vs. Ag/AgCl). Data are presented as mean  $\pm$  s.e.m.; two-tailed Student's *t*-test ( $n = 3$ , for each group).

Next, the mechanically-evoked  $\text{Ca}^{2+}$  and NO responses were characterized, combined with GsMTx4 to further investigate the role of Piezo1 in mechanotransduction. In a  $\text{Ca}^{2+}$ -free bath solution, mechanical stimulation still induced an increase in intracellular  $\text{Ca}^{2+}$  (Fig. 6e and Supplementary Fig. 23), demonstrating the contribution from the release of intracellular calcium stores. This was further supported by the negligible differences in peak fluorescence intensity between the 10% mechanical deformation group and non-deformed control, when MC3T3-E1 cells were pretreated with BAPTA-AM to chelates intracellular  $\text{Ca}^{2+}$  (Supplementary Fig. 24). Given that cells reside in a  $\text{Ca}^{2+}$ -containing physiological environment in vivo, 10% deformation was applied to the MRnM@FeP/s-P sensor in a 2 mM  $\text{Ca}^{2+}$  bath solution, which led to a further elevation in intracellular  $\text{Ca}^{2+}$  levels. In contrast, pretreatment with the GsMTx4 significantly attenuated  $\text{Ca}^{2+}$  influx (Fig. 6e and Supplementary Fig. 23). Therefore, mechanical stimulation-induced intracellular  $\text{Ca}^{2+}$  elevation could be attributed to two ways:  $\text{Ca}^{2+}$  influx mediated by the activated Piezo1 channels and the release of intracellular calcium stores. Meanwhile, the MRnM@FeP/s-P sensor recorded a significant increase in current response from cells incubated with 2 mM  $\text{Ca}^{2+}$ , and a sharp decrease in current response from GsMTx4-treated cells, compared to the cells under  $\text{Ca}^{2+}$ -free condition (Fig. 6f). Quantitative analysis showed that the calculated amounts of mechanically-evoked NO were approximately 1.2 nmol (2 mM  $\text{Ca}^{2+}$  group), 0.1 nmol (GsMTx4 group) and 0.7 nmol (0 mM  $\text{Ca}^{2+}$  group), respectively (Fig. 6g). And the fluorescence intensity of intracellular NO exhibited a similar trend to the results of electrochemical detection (Supplementary Fig. 25). The consistent trends observed in  $\text{Ca}^{2+}$  and NO responses suggest that the activation of mechanosensitive channels (including Piezo1) contributes to deformation-induced elevation of intracellular  $\text{Ca}^{2+}$  level and NO production (Fig. 6e, g). Collectively, our study reveals that Piezo1 mechanosensitive ion channels are expressed in MC3T3-E1 cells and can be rapidly activated by mechanical stimulation, thereby participating in the elevated intracellular  $\text{Ca}^{2+}$  levels and subsequent NO release through NOS activation (Fig. 6h).

### Magnetic manipulation and real-time monitoring of NO from tibia in vivo

To demonstrate the potential of the MRnM@FeP/s-P sensor for in vivo applications, the sensor was implanted into the mid-shaft of a rat's tibia to monitor NO release under both chemical and mechanical stimuli (Fig. 7a). Notably, many regular signals appeared in the baseline of the amperometric response, which corresponded to the electrophysiological activities of the rat. The administration of isoprenaline via the tail vein accelerated the heart rate, reducing the inter-peak interval from 0.92 to 0.62 s, consistent with the observed cardiac cycles (Fig. 7b and Supplementary Fig. 26). When L-arginine (L-Arg, NO precursor, 5 mM) solution was added to the tissues surrounding the tibia, MRnM@FeP/s-P sensor recorded a rapid increase in current, which subsequently returned to the baseline within 200 s. While with the pretreatment of L-NMMA (1 mM), the addition of L-Arg did not result in a significant change in current response, which was comparable to the untreated control group (Fig. 7c), confirming the successful detection of NO production induced by L-Arg.

As a key weight-bearing bone, the tibia is susceptible to mechanical damage caused by physical activity or external impact. To investigate the biochemical response of the tibia under dynamic mechanical conditions, we applied controlled compression stimulation to the distal end of the tibia using surgical forceps. Simultaneously, the MRnM@FeP/s-P sensor, placed at the mid-shaft of the tibia, monitored the increase of NO in real time (Fig. 7d). Furthermore, the magnet was approaching to the tibia to magnetically actuate the implanted MRnM@FeP/s-P sensor (Fig. 7a). Upon magnetic stimulation, the sensor recorded a rapidly rising current signal in the amperometric curve (Fig. 7e). Quantitative analysis, performed by subtracting the current signals of the L-NMMA group, showed that the amount of magnetic actuation-evoked NO was 0.35 nmol (Fig. 7f). These results demonstrated the capability of MRnM sensors for both mechanical manipulation and real-time detection of biochemical signals in vivo.

To evaluate the host tissue response and functional stability of the MRnM@FeP/s-P sensor, histological and electrochemical characterization were conducted after 2-weeks of implantation. Hematoxylin-

Eosin (H&E) staining image showed the minimal inflammatory cell infiltration around the sensor (brown areas, Supplementary Fig. 27), demonstrating the good biocompatibility and great potential for long-term implantation. When MRnM@FeP/s-P sensors were took out from the subcutaneous tissue after 1 and 2 weeks of implantation, their electrochemical stability were evaluated by recording the CV responses in  $K_3[Fe(CN)_6]$  solution (Supplementary Fig. 28). Compared to the original electrodes, the charging current of 1-week implanted electrodes was significantly reduced, while the peak current still retained approximately 70%. Nevertheless, the electrochemical performance of 2-weeks implanted electrodes exhibited substantial degradation, which is likely attributed to the surface passivation caused by the adsorption of biological molecules. To mitigate biofouling, hydrogel coatings and hydrophilic molecule functionalization could be implemented on the electrode surface<sup>24,65</sup>.

## Discussion

In summary, we reported a MRnM biosensor that currently enables remote, controllable mechanical stimulation and real-time electrochemical monitoring of biochemical responses of both living cells in vitro and tissues in vivo. The sensor was fabricated via electrospinning magnetic PU/Fe<sub>3</sub>O<sub>4</sub> nanomesh, and subsequent assembling functionalized and tunable PEDOT (doped with FeTCP, CoPcS and Pt NPs) as the sensing elements. Under an external magnetic field, this MRnM sensor exhibited excellent magnetic responsiveness and stable electrochemical sensing performance. As a proof of concept, we demonstrated the feasibility of the described sensor for the magnetically-actuated deformation of osteoblasts and simultaneous monitoring of the ensuing NO release with the involvement of Piezo1 channel activation, as well as remotely mechanical manipulation of the tibia in vivo and real-time detection of NO.

The proposed biosensor exhibits prominent mechanical softness, magnetic responsiveness, and versatility in fabrication methods, along with several potential avenues for expanding its applications in the future. For instance, incorporating tailored materials (e.g., ionophore, nano-enzyme, single-atom and biomimetic molecular catalysts) into the sensing coatings could endow MRnM sensors with high specificity and sensitivity for in situ analysis of various other targets, such as ions (e.g., Ca<sup>2+</sup> and K<sup>+</sup>), electroactive biomolecules (e.g., H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>S and catecholamines) and non-electroactive metabolites (e.g., glucose and ATP). From the perspective of magnetic actuation, the MRnM sensor could be precisely located at the targeted tissue or organ in vivo through magnetic navigation<sup>66</sup>. The mechanical regulation capability of the sensor would facilitate the repair of tissues, such as bone and cartilage<sup>67</sup>, as well as promote the healing of injured tissues or modulate inflammation in chronic diseases<sup>68</sup>, offering a promising tool for therapeutic intervention. Additionally, the MRnM sensor provides an alternative strategy for single-cell manipulation and detection with high spatiotemporal resolution by controlling specific nanofibers (as demonstrated in Fig. 2g), which allows local manipulation of an individual cell within a population. Furthermore, given its remarkable softness and stable recording capabilities, the MRnM sensor integrated with a wireless transmission module is expected to function as an injectable electronic device for electrochemical and electrophysiological monitoring of target tissues and mechanical regulation of their functions as a reliable magnetism therapy.

## Methods

### Materials and instruments

PU was purchased from Huangjiang Shengbang (Dongguan, China). Fe<sub>3</sub>O<sub>4</sub> NPs were purchased from Yuanye Bio-Technology Co., Ltd. (Shanghai, China). DMF, THF and dimethyl sulfoxide (DMSO) were purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). PEDOT:PSS (Clevios PH1000) was purchased from Wuhan

Zhuojia Technology Co., Ltd. (Wuhan, China). FeTCP and D-sorbitol were purchased from Aladdin Industrial Co., Ltd. (China). The PDMS prepolymer and cross-linker were obtained from Momentive Performance Materials (Waterford, NY, U.S.A.). L-Arginine (L-Arg, A8094), Calcein-AM, propidium iodide (PI), Cell Tracker Green CMFDA and Hoechst 33258 were purchased from Sigma-Aldrich (Germany). Total NOS inhibitor L-NMMA, fluorescent NO probe (DAF-FM DA) and calcium ion fluorescence probe (Fluo-4 AM) were purchased from Beyotime Biotechnology (Shanghai, China). Anti-Piezo1 antibody (ab128245) was purchased from Abcam Co. Ltd. (U.K.). GsMTx4 (HY-P1410), Yoda1 (HY-18723), BAPTA-AM (HY-100545) and isoprenaline (420355) were purchased from MedChemExpress Co., Ltd. (U.S.A.). DyLight 488 (A23220) conjugated goat anti-rabbit IgG was bought from Abbkine Scientific Co., Ltd. (Wuhan, China). The size of the NdFeB permanent magnet is 14 × 14 × 9 mm<sup>3</sup>, and the magnetic induction intensity on the surface of the magnet is 630 mT. Ultrapure water (Millipore, 18.0 MΩ·cm) was used in all experiments. Mouse embryonic pre-osteoblast (MC3T3-E1 cells) was purchased from Hunan Fenghui Biotechnology Co., Ltd. (Changsha, China). α-minimum essential medium (α-MEM) was purchased from Procell Life Science & Technology Co., Ltd. (Wuhan, China). Fetal bovine serum, penicillin and streptomycin for cell culture were obtained from GIBCO (U.S.A.). Cell culture flasks were purchased from Jet BioFiltration Co., Ltd. (Guangzhou, China).

Electrospinning device (Qingzi Nano-E05) was bought from Foshan Qingzi Co., Ltd. (Foshan, China). Cantilever mixer was bought from IKA-Werke GmbH & Co. KG (RW 20 digital, Germany). Plasma cleaner was bought from Harrick Plasma (PDC-002, U.S.A.). Scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDX) images were taken by a field-emission scanning electron microscope (TESCAN CLARA, Czech Republic) equipped with an energy-dispersive X-ray spectroscopy spectrometer (Oxford Ultim Extreme). Transmission electron microscopy (TEM) images were obtained on a transmission electron microscope (JEOL JEM-F200, Japan). Energy-dispersive A Vibrating samples magnetometer was exploited to properly characterize the samples in terms of saturation magnetization and hysteresis loops. The Young's modulus was implemented by a Cell Tester (SI-CTS200, WPI, Germany). Atomic force microscope (AFM) images were recorded in tapping mode using an Atomic Force Microscope (Park NX10, Korea). X-ray photoelectron spectroscopy (XPS) measurements were conducted with a photoelectron spectrometer (ESCALAB250Xi, Thermo Fisher Scientific). The C 1s peak (284.6 eV) was chosen as a reference to calibrate binding energies, and Al Kα X-ray radiation was used as the X-ray source. The UV-vis absorption spectra were recorded on a UV-3600 spectrophotometer with 90% ethanol and 5% (v/v) DMSO as reference. Electrochemical measurements were conducted by a CHI 660E electrochemical workstation (CHI Instruments) with a reference electrode (Ag/AgCl) and a counter electrode (Pt). Zetasizer Nano ZSP (Malvern Instruments, Malvern, U.K.) was utilized for measuring zeta potential with a detection angle of 173° at 25 °C. The Nano ZSP used a 10 mW He-Ne laser operating at a wavelength of 633 nm. LSM 900 laser confocal microscopy (Zeiss, Germany) was utilized for fluorescence imaging.

### Fabrication of MRnM

Firstly, electrospinning solutions were prepared by uniform mixing different contents of Fe<sub>3</sub>O<sub>4</sub> NPs with PU (0.4 g) in DMF/THF (4 mL) solution (v/v = 1:3) under stirring at 500 rpm for 1 h. Then, the solution was loaded into a 10 mL syringe (tip diameter = 0.7 mm) and electrospun at 16 kV for 30 min with a feeding rate of 0.8 mL h<sup>-1</sup>. The electrospun nanofibers were collected at a distance of 10 cm by a metal drum rotating at 1000 rpm. To fabricate self-supporting MRnM, the collected nanomesh cut into a size of 12 mm × 20 mm and transferred onto a PDMS substrate with a hollow structure (15 mm × 15 mm).

### Fabrication of functionalized PEDOT and MRnM sensors

First, D-sorbitol (5 wt%) was added into commercial PEDOT:PSS solution and sonicated for 5 min to ensure complete dissolution (s-PEDOT). The catalysts FeTCP (0.2 mM), CoPcS (0.5 mM), and Pt NPs (0.2 g mL<sup>-1</sup>) were separately dissolved in anhydrous ethanol. Next, the s-PEDOT solution and the catalyst-containing ethanol solution were mixed at a 2:8 (v/v) ratio and sonicated for 2 h at room temperature to facilitate the interaction between the catalyst and PEDOT. Finally, 5% (v/v) DMSO was added to further enhance the conductivity of the functionalized PEDOT solution.

Results from finite element analysis indicated that stress distribution at the center area of the MRnM showed better uniformity than the boundary regions, and therefore the active electrode area of PEDOT:PSS was defined to be 8 mm × 8 mm during the fabrication process. Specifically, a thin PDMS masking film with a hollow square (8 mm × 8 mm) was covered onto the MRnM surface, followed by a 5-min plasma treatment to enhance hydrophilicity. Then, a functionalized PEDOT solution was soak-coated onto the exposed area for 20 min. After removing the PDMS mask, the defined 8 mm × 8 mm active region was retained for electrochemical sensing, followed by annealing at 110 °C for 10 min to complete the MRnM sensor.

### Tensile experiment

Uniaxial tensile test was used to evaluate the mechanical properties of nanomesh by a Cell Tester. The two ends of the nanomesh were fixed on the stretching device, which was connected to a high-sensitivity force transducer of the Cell Tester, and stretched at a slow and uniform speed until the nanomesh was broken. The data of tension ( $F$ ) was recorded by computer software, and Young's modulus ( $E$ ) was calculated according to the following equation:

$$\text{Young's modulus}[E] = \frac{\sigma}{\varepsilon} = \frac{FL}{S \cdot \Delta L} \quad (1)$$

where  $F$  is the tension of pulling off nanomesh,  $L$  is the initial length of the nanomesh,  $S$  is the sectional area of the nanomesh and  $\Delta L$  is the relative elongation length.

### Preparation of NO solution

NO was prepared based on the disproportionation reaction of NaNO<sub>2</sub> as reported previously<sup>34</sup>. In brief, H<sub>2</sub>SO<sub>4</sub> solution (25 mL, 2 M) was dropped into NaNO<sub>2</sub> solution (50 mL, 4 M) at a rate of 0.5 mL min<sup>-1</sup>, and the generated gas passed through NaOH solution (4 M) to eliminate other NO<sub>x</sub>. Then the purified NO was introduced into the PBS solution for 60 min to obtain a saturated solution of NO (1.8 mM). Standard solutions of different concentrations were obtained by diluting the saturated solution with PBS solution. Notably, the entire experimental setup and solutions were pre-purged with nitrogen (N<sub>2</sub>) for oxygen elimination to ensure the anaerobic environment in the NO generation and collection procedures. All the standard solutions were freshly prepared and stored in a sealed container at 4 °C.

### Calibration of the MRnM@FeP/s-P sensor for NO

A series of standard NO solution with varying concentrations were obtained by gradually diluting the prepared NO-saturated solution. The calibration was performed by gently adding the standard NO solution into PBS (pH ~ 7.4) without stirring.

### Cells culture

MC3T3-E1 cells were cultured in  $\alpha$ -MEM culture medium added with fetal bovine serum (10%) and penicillin-streptomycin (1%) in a humidified incubator (37 °C and 5% CO<sub>2</sub> atmosphere). Before cell seeding, the MRnM@FeP/s-P sensor was thoroughly sterilized with ultraviolet exposure overnight. MC3T3-E1 cells were seeded onto the electrodes

at a density of approximately  $5 \times 10^5$  cell cm<sup>-2</sup>. To confine cell specifically to the electrode region, a pre-prepared PDMS frame (8 mm × 8 mm × 3 mm) was carefully aligned to the electrode surface prior to cell seeding. The electrodes inoculated with cells were placed in the incubator for 12 h to allow cells to adhere tightly to the electrode. Before electrochemical detection, the loosely adherent cells were washed away with sterile PBS.

### Cell viability experiment

To evaluate the biocompatibility of the sensor, the incubation period was prolonged to 36 h with a lower cell seeding density ( $4 \times 10^5$  cells cm<sup>-2</sup>) than that used for electrochemical detection ( $5 \times 10^5$  cells cm<sup>-2</sup>, 12 h). The viability of MC3T3-E1 cells was assessed by fluorescent live/dead cell markers Calcein-AM (2  $\mu$ g mL<sup>-1</sup>) and PI (3  $\mu$ g mL<sup>-1</sup>). For tracking the cells during synchronous deformation with the underlying MRnM@FeP/s-P sensor, MC3T3-E1 cells were preloaded with the Cell Tracker Green CMFDA (1:1000).

### Fluorescence imaging of Ca<sup>2+</sup> and NO in MC3T3-E1 cells

For probing intracellular Ca<sup>2+</sup> and NO levels, MC3T3-E1 cells were incubated with Ca<sup>2+</sup> fluorescent probe Fluo-4 AM (2  $\mu$ M) or NO fluorescent probe DAF-FM DA (5  $\mu$ M) for 1 h in advance and washed with sterile PBS 3 times. For the inhibition experiment, MC3T3-E1 cells were co-incubated with BAPTA-AM (20  $\mu$ M) and Fluo-4 AM (2  $\mu$ M) for 1 h.

### Immunofluorescence staining

For Piezo1 immunostaining, MC3T3-E1 cells were firstly fixed with paraformaldehyde (4%) for 15 min and permeabilized with Triton-X 100 (0.1%) for 5 min, then blocked with normal goat serum (1.5%) for 45 min. Next, the cell samples were incubated with anti-Piezo1 antibody (1:100) overnight at 4 °C followed by a further incubation with a DyLight 488 conjugated goat anti-rabbit IgG (1:1000) and Hoechst 33258 (10  $\mu$ g mL<sup>-1</sup>) at 37 °C for 1 h. Before observation, the unbound dyes were washed with sterile PBS for 3 times.

### Western Blot assay

Western Blot assay was performed according to standard protocols. The following antibodies were used: Actin antibody (ABclonal, AC026, 1:10000) and Piezo1 antibody (Abcam, ab128245, 1:1000).

### Real-time monitoring of NO release from MC3T3-E1 cells

To monitor the mechanically-evoked NO released in real time, the MRnM@FeP/s-P sensor with MC3T3-E1 cells cultured thereon was connected to an electrochemical workstation via conducting wires for simultaneous amperometric monitoring. The magnet was placed above the electrode, and the electrode was driven to deform rapidly along the direction of the magnetic field when the magnet was approaching. For the inhibition experiment, MC3T3-E1 cells were pretreated with L-NMMA (1 mM) for 20 min or GsMTx4 (10  $\mu$ M) for 1 h. Yoda 1 (40  $\mu$ M, dissolved in DMSO and diluted with PBS solution) was added to the MC3T3-E1 cells bath to activate Piezo1 protein.

### In vivo experiments

All animal procedures were carried out strictly according to protocols (No. WQ20210375) approved by the Institutional Animal Care and Use Committee (IACUC) of the Animal Experiment Center of Wuhan University (Wuhan, China). Sprague-Dawley (SD) rats were bought from Hubei provincial laboratory animal public service center (Wuhan, China). Before in vivo experiments, the MRnM@FeP/s-P sensor, Ag/AgCl reference electrode and Pt counter electrode were sterilized through ultraviolet irradiation for 12 h, and the surgical instruments were sterilized. SD rats were anesthetized with sodium pentobarbital solution, followed by the removal of skin and subcutaneous tissue to expose the tibia.

For in vivo electrochemical detection, the MRnM@FeP/s-P sensor was closely attached to the surface of the tibia, and the Ag/AgCl reference electrode and Pt counter electrode were placed in the interstitial fluid on the tissue surface. The amperometric method was performed to detect NO released under mechanical stimulation or local chemical stimulation. The tissues were pretreated with L-NMMA (1 mM) for 20 min. The final concentration of isoprenaline and L-Arg were 0.5 mg kg<sup>-1</sup> and 5 mM, respectively.

To evaluate the biosafety of the MRnM@FeP/s-P sensor, the sensor was implanted into the subcutaneous tissue of the SD rat hindlimb, followed by suturing. On day 14 post-implantation, tissue samples were collected for H&E staining to assess the inflammatory response. The control group consisted of tissues that were not implanted with a sensor but sutured, and were stained with H&E for comparison.

### Quantitative analysis

The NO released by cells was monitored in real time by the electrochemical method. To convert the obtained signals into quantitative data, the areas under the obtained amperometric curves were integrated to calculate the charge ( $Q$ ) according to Eq. (2), and the background contribution from mechanical disturbances was subtracted to isolate the electrochemical signal.

First, the electrochemical signal was integrated after subtracting the baseline.

$$Q = \int i dt \quad (2)$$

where  $i$  is the current and  $t$  is time.

Then, according to Faraday's law (Eq. (3)), the corresponding charge can be converted to the molar quantities of NO.

$$n = \frac{Q}{zF} \quad (3)$$

where  $n$  is the molar amount of NO,  $F$  is the Faraday constant ( $9.65 \times 10^4$  C mol<sup>-1</sup>), and  $z$  is the number of transferred electron (for NO oxidation,  $z = 3$ ).

### Statistical analysis and reproducibility

At least three independent experiments of each group have been performed and produced consistent results. Each point in the statistical chart represents a specific value from independent experimental replicates. For comparisons between two groups, a two-tailed Student's  $t$ -test was performed to determine statistical significance. For the analysis involving three groups, one-way ANOVA followed by the least significant difference (LSD) post-hoc test was conducted using IBM SPSS Statistics 27. Differences of  $*p < 0.05$  denote significance compared with other groups. Fluorescence images were quantitatively analyzed using ImageJ software. The sample sizes (biological replicates), specific values of independent experiments, error bars of the mean values (s.e.m.) and  $P$  values of statistical analyses are detailed in each figure legend. SEM, TEM and corresponding EDX imaging, AFM imaging, fluorescence staining and immunofluorescence staining were repeated independently at least three times with similar results.

### Ethics declarations

Every experiment involving animals has been carried out following a protocol approved by an ethical commission.

### Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

### Data availability

All data supporting the findings of this study are available within the article and its supplementary files. Any additional requests for information can be directed to and will be fulfilled by the corresponding authors. Source data are provided with this paper.

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## Acknowledgments

This work was supported by the National Natural Science Foundation of China (grants No. 22404127 to Y.-L.L. and 22122408 to Y.-L.L.) and National Key Research and Development Program of China (2022YFA1104802 to W.-H.H.).

## Author contributions

K.-Q.J. carried out the experiments and wrote the manuscript. T.-C.S. assisted in the in vivo experiments. Z.-X.Z. performed the FEA model. J.-D.L. assisted in the fabrication of the electromagnetic needle and local magnetic manipulation. Y.Z., W.-T.F. and J.Y. contributed to the discussion. G.-Y.H., W.-H.H., and Y.-L.L. supervised the project and revised the manuscript.

## Competing interests

The authors declare no conflict of interest.

## Additional information

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41467-025-63623-8>.

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**Peer review information** *Nature Communications* thanks Hongyan Gao, María C. Serrano, and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

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