

Influence of cell force-driven piezoionic hydrogels on the migration of cancer cells

Xiaoru Li¹, Ting Zhang¹, Chen Wang¹, Zihan Qiao¹, Qingchuan Zhang¹✉, and Shangquan Wu^{1,2}✉

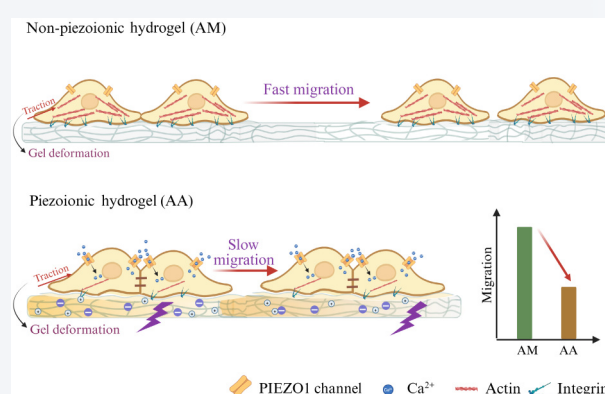
¹CAS Key Laboratory of Mechanical Behavior and Design of Material, Department of Modern Mechanics, University of Science and Technology of China, Hefei 230027, China

²State Key Laboratory of Nonlinear Mechanics, Institute of Mechanics, Chinese Academy of Science, Beijing 100190, China

 Cite this article: *Nano Research*, 2026, 19, 94908694. <https://doi.org/10.26599/NR.2026.94908694>

ABSTRACT: Cancer metastasis presents a formidable clinical challenge, demanding innovative therapeutic approaches. Compared to normal cells, the enhanced migratory capacity of malignant cancer cells plays a pivotal role in the metastatic process. Targeting this differential motility to inhibit migration may offer a novel strategy for cancer treatment. We found that the piezoionic hydrogels significantly inhibited the migration of human hepatocellular carcinoma cells (Huh-7) which are characterized by high migratory capacity, with minimal impact on normal cell migration. Cell adhesion genes like *ICAM1* increased and N-cadherin decreased on the piezoionic hydrogel. Besides, piezoionic hydrogels induced calcium overload in cancer cells by activating Piezo1 and promoting excessive calcium influx, which can disrupt mitochondrial function and compromise cytoskeletal integrity, ultimately hindering cell migration. Crucially, our research has pioneered the validation of a novel strategy: harnessing the inherent migratory properties of cancer cells to suppress their own migration, while exerting minimal inhibitory effects on normal cells with weaker migratory capabilities, may offer a superior method and strategy for specifically targeting and inhibiting malignant cancer cell metastasis.

KEYWORDS: piezoionic hydrogels, cell migration, calcium ion, migration inhibition



1 Introduction

Metastasis of malignant tumors is a major cause of cancer treatment failure and is difficult to eradicate once it occurs [1]. In this process, cancer cells detach from the primary tumor site, invade the surrounding tissues, survive in the circulatory system, and eventually colonize distant organs, constituting the most challenging aspect of cancer treatment [2, 3]. Among them, the migratory ability of cancer cells is the central driver of invasion and metastasis [4, 5]. Current clinical practice primarily relies on chemotherapeutic agents for cancer treatment, however, safely administered doses often fail to achieve complete patient cure, while supra-therapeutic levels can result in significant damage to

surrounding healthy tissues [6–9]. Developing methods that can specifically inhibit cancer cell metastasis while causing minimal damage to normal cells holds significant importance for cancer therapy.

Extensive research has demonstrated that electrical stimuli influence cellular behaviors, including the contact guidance-directed migration of neural stem cells towards neuroblasts, wherein cell type and electric field parameters dictate migration towards either the cathode or anode [10, 11]. Furthermore, low-intensity, prolonged electrical stimulation can promote the proliferation of certain cell types, whereas high-intensity or extended electrical stimulation may inhibit proliferation, underscoring the profound interplay between electric fields and cellular life activities [12–14].

Piezoelectric materials can achieve electrical stimulation through their piezoelectric properties. For instance, L. Ricotti et al. [15] promoted chondrogenesis by ultrasound-exciting piezoelectric nanocomposite hydrogels. Wang et al. [16] developed a novel ultrasound-responsive piezoelectric composite hydrogel that facilitates local neurovascular regeneration through acoustic-to-

Received: December 30, 2025; Revised: March 30, 2026

Accepted: March 31, 2026

✉Address correspondence to Qingchuan Zhang, zhangqc@ustc.edu.cn; Shangquan Wu, wushq@ustc.edu.cn

electric conversion, while simultaneously inhibiting bacterial activity and accelerating diabetic wound healing. Luo et al. [17] engineered a dual-network piezoelectric hydrogel that utilizes its tunable acoustic-electric effect for wound sterilization and sustained promotion of human fibroblast proliferation and migration. It is evident that conventional piezoelectric materials are typically rigid and require external ultrasound for activation. Although piezoelectric composite hydrogels can also have a soft matrix, the cell traction force generated by actin-myosin contractility and focal adhesion dynamics is usually in the range of several nanonewtons to several hundred nanonewtons, corresponding to approximately 10–1000 pascals of local matrix stress [18–20]. Traditional piezoelectric hydrogels made of polyvinylidene fluoride (PVDF) or barium titanate (BaTiO_3) composites, relying solely on the traction force between cells, are insufficient to generate measurable electrical signals, external ultrasonic stimulation or mechanical stimulation is also required to generate significant electrical signals [21–23]. This indicates that there is a critical gap of one to two orders of magnitude between the material sensitivity and the physiological force range. This mismatch fundamentally limits the ability of piezoelectric composite hydrogels to convert cellular mechanical signals without external intervention. In contrast, piezoionic hydrogels utilize the redistribution of ions in the polymer network during deformation to generate electrical signals in response to pressures as low as several pascals [24, 25]; this is comparable to the traction forces generated by cells. This inherent sensitivity makes piezoionic hydrogels particularly suitable for capturing weak mechanical stimuli driven by cells in the absence of any external stimulation.

Owing to its remarkably low stiffness, this material can transduce subtle cellular traction forces into electrical signals, which then exert feedback on the cells, thereby modulating their behavior. Cancer cells, exhibiting greater motility and exerting larger forces on the surrounding matrix compared to normal cells [26–28], have the potential to generate more pronounced electrical stimuli relative to their normal counterparts. This difference in electrical properties caused by cell movement could potentially lead to differences in their states or behaviors. Based on this differential response, we aim to investigate the distinct behaviors of cancer and normal cells on the piezoionic hydrogel, with the ultimate goal of providing guidance for the design of novel anti-cancer strategies.

In this study, we developed a cell migration system based on piezoionic hydrogels (acrylic acid is the main active ingredient, AA) for the analysis of cancer cells movement behaviors. Upon generating localized traction forces via integrin-mediated adhesion, cancer cells induce an intrinsic piezoelectric potential that is directly proportional to the applied stress intensity within the material. The establishment of this piezoelectric platform based on cellular self-feedback creates a unique platform for closed-loop regulation of "cell movement–material electrical response–cell migration" (Fig. 1(b)). We systematically investigated the regulatory mechanisms of endogenous piezoelectric fields on cancer cell migration patterns (Fig. 1). Coupled with calcium imaging and cell migration analysis, we have elucidated the molecular mechanisms by which piezoelectric potentials mediate cell movement remodeling through voltage-gated ion channels. This finding not only offers a novel paradigm for understanding cancer cell mechanosensing but also may present a new avenue for anti-cancer strategies.

2 Results and discussion

2.1 Material properties and inhibition of cell migration

In order to stimulate piezoelectric signals by the cell's own traction, we referred to previous studies and adopted piezoionic hydrogels that have better biophilicity and respond better to the cell's traction. This type of hydrogel is soft enough to convert the cell's own traction force into electricity [29]. Pressure was applied and the cations were displaced to produce a voltage response (Fig. S1(a) in the Electronic Supplementary Material (ESM)). We applied a force of 50 g weights and ultrasound stimulation on the prepared hydrogel, and the oscilloscope results showed that AA gels obtained obvious voltage fluctuations, verifying that the piezoionic hydrogels (acrylic acid is the main active ingredient, AA) do indeed have piezoelectric properties (Figs. S1(b)–S1(d) in the ESM). The polyacrylamide hydrogels (acrylamide is the main active ingredient, AM) have no piezoelectric effect, so we use AM as the control group for this study's experiments. Considering that the hydrogel hardness may also have a certain impact on the cellular behavior, the modulus of the AA gel and the AM gel were made to be basically the same by adjusting the content of the hydrogel

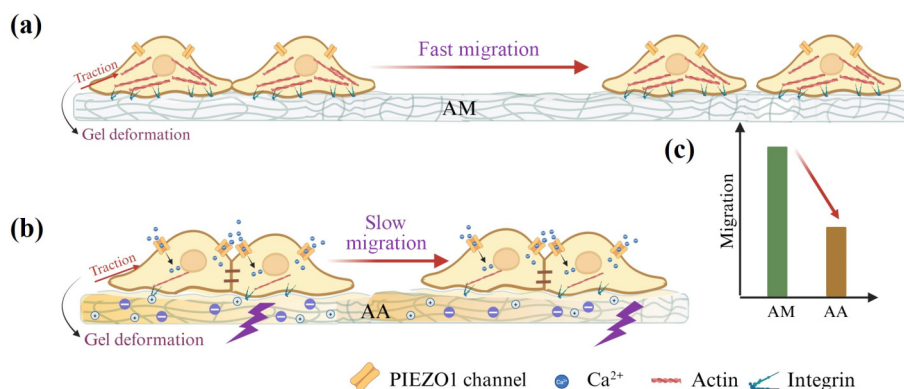


Figure 1 The effect of piezoionic hydrogel (AA) and polyacrylamide hydrogels (AM) on cell migration. (a) The migration of Huh-7 on AM gels. (b) The migration of Huh-7 on AA gels. Upon adhesion to the AA gel substrate, cellular locomotion generates traction forces that are transmitted to the gel matrix. This mechanical deformation of the hydrogel subsequently elicits an electrical stimulus experienced by the cells. In response, the ion channel Piezo1 is activated, leading to an influx of calcium ions. Concurrently, there is a decrease in the abundance of actin and paxillin, resulting in impaired cellular migration. AA gels inhibit N-cadherin, resulting in stronger intercellular adhesion on cells on AA gels compared to cells on AM gels. This consequently leads to reduced cellular migration, which is likely a significant factor contributing to the slower scratch recovery. (c) The inhibition of cell migration on AA gels compared to AM gels.

monomers, which was around 3 kPa (Fig. S1(e) in the ESM). The pictures taken by scanning electron microscopy (Figs. S1(f) and S1(g) in the ESM) and our previous research has shown that both these two gels exhibited a porous structure [29]. The pore diameters of these hydrogels range from 20 to 80 μm . Particularly for the AA gel, these large and interconnected pores provide a smooth pathway for the movement of ions during the mechanical deformation of the hydrogel. When cell traction force is applied to the cells located on the AA hydrogel substrate, the resulting local deformation enables the mobile ions to pass through this pore network more easily, thereby generating significant charge separation and interface electric fields. Furthermore, we also conducted a cell membrane potential detection experiment. Using the membrane potential-sensitive fluorescent probe bis-(1,3-dibutylbarbituric acid)trimethine oxonol (DiBAC₂⁽³⁾), we labeled the migrating cells on the two groups of hydrogels. The results showed that the cell membrane potential on the AA gel was significantly higher than that on the AM gel. This also indicates that a local potential change did occur at the cell-hydrogel interface and the cells sensed the electrical signal stimulation at the interface (Figs. S3(b) and S3(c) in the ESM).

We selected human hepatocellular carcinoma cells (Huh-7) cells as the primary model for this study. From scratch experiments, we observed that the rate of healing of scratches in cells on AA gels was much less than that on AM gels, both at 12 and 24 h (Figs. 2(a) and 2(b)). To verify the universality of the results, we conducted scratch experiments using another cancer cells (Hep-G2) and found that AA gels were also able to significantly inhibit the migration of cancer cells ("Control" in Figs. 2(f) and 2(h)). It is reported that both cell migration and proliferation abilities can affect the wound healing behavior. Therefore, in order to determine the main causes of the different wound healing behaviors exhibited by Huh-7 cells under the specified culture conditions, we measured the proliferation ability of these cells under the specified conditions. The cells were stained with a 5-ethynyl-2'-deoxyuridine (EDU) experiment (Figs. S2(a) and S2(b) in the ESM), and the results indicated no significant difference in proliferation of cells between cells on AA gels and AM gels. This approach effectively rules out potential confounding effects on scratch results from cell proliferation, suggesting that the slow recovery of scratches of AA gels is mainly due to the slow cell migration on the surface of the gel. To further investigate the effect of AA gels on cell movement, we performed single-cell migration experiments, and cells on AM gels moved more widely and faster than cells on AA gels (Figs. 2(d) and 2(e)), indicating that AA gels do indeed inhibit cancer cell migration. To provide a more comprehensive characterization of cell migration behavior, we conducted more trajectory analyses, including net displacement, migration consistency, and directional persistence (Figs. S3(d) and S3(e) in the ESM); cells cultured on AA gels exhibited notably lower net displacement values compared to those on AM gels, indicating that piezoionic stimulation can inhibit greater overall translocation. The migration consistency index revealed that a subset of cells on AA gels maintained more linear trajectories, reflecting a more directed migratory mode. Furthermore, the directional persistence (mean cos) values were generally positive for both groups, yet cells on AA gels showed a high direction persistence. Collectively, these multi-parameter analyses demonstrate that piezoionic hydrogels influence not only the speed but also the directionality and persistence of cell migration. However, by co-culturing normal cells (THLE-2) with

AM gels and AA gels and performing single-cell migratory analysis, the results indicate that, compared with AM gels, the migration velocity of normal cells on AA gels shows almost no difference (Figs. 2(c) and 2(g)). Consequently, in contrast to cancer cells, the inhibition of normal cell migration by AA gels is almost negligible. This suggests that AA gels have potential as a dressing to suppress tumor metastasis, and the AA gels used herein exhibits selective targeting of cancer cells, with relatively little effect on normal cells.

In tumor pathology, the epithelial-mesenchymal transition (EMT) is the main cause of infiltrative metastasis of malignant tumors. After the occurrence of EMT, the migratory ability or motility of the cells significantly increased [30]. To further validate the anti-migratory effect of AA hydrogel, 10 ng/mL TGF- β 1 was introduced to induce EMT. To validate successful EMT induction, reverse transcription quantitative polymerase chain reaction (RT-qPCR) analysis was performed on control and TGF- β 1-treated cells. TGF- β 1 treatment resulted in a significant downregulation of E-cadherin and ZO-1 and a significant upregulation of vimentin and N-cadherin at the mRNA level compared to untreated controls (Fig. S2(e) in the ESM), confirming the successful induction of EMT under our experimental conditions. When cells were not exposed to TGF- β 1, their migration became faster compared to cells that had not undergone EMT ("Control" in Figs. 2(f) and 2(h)). Furthermore, cells cultured on AA gels still have significantly less migration compared to cells on AM gels ("TGF- β 1" in Figs. 2(f) and 2(h)). Even following EMT, cellular migration on AA gels remained significantly lower than that on AM gels from non-EMT cells, indicating a potent inhibitory capacity of AA-gels on carcinoma cell motility. This confirms a pronounced inhibitory effect of AA hydrogel on cell migration. This conclusion was also verified in Huh-7 cells (Figs. S2(c) and S2(d) in the ESM); cell migration on AA gels was also significantly slower than that on AM gels when adding TGF- β 1 and cell migration on AA gels with TGF- β 1 was still slower than that on AM gels without TGF- β 1. This once again demonstrates that AA gels can effectively inhibit the migration of cancer cells, and the inhibitory effect is significant for different types of cancer cells.

2.2 Intercellular adhesion

RNA sequencing (RNA-seq) experiments were conducted on Huh-7 cells to compare those on AA gels and AM gels. It was found that there are some genetic changes in the cells on the two types of hydrogels (Fig. 3(a)). *ICAM1* can promote adhesion between cells at the inflammatory site and hinder tumor and metastasis, and the *TRIM8* gene can inhibit the invasion of liver cancer cells. They had higher expression in the AA group (Fig. 3(b)). To confirm that RNA-seq experiments transcriptional changes correspond to functional protein-level alterations, immunofluorescence test was performed for ICAM-1, consistent with the transcriptomic data, ICAM-1 protein expression was significantly elevated in cells on AA hydrogels (Figs. 3(c) and 3(e)). These changes led to enhanced cell adhesion and inhibited migration on AA gels. As a glycosylated transmembrane protein, N-cadherin modulates cellular migration capacity by regulating intercellular mechanical adhesion [31]. The gain of N-cadherin promotes invasion, migration, and metastasis in cancer cells [32, 33]. Through immunofluorescence staining, it can be observed that the content of N-cadherin in cells on the AM gel is significantly higher than that on the AA gel (Figs. 3(d) and 3(e)). AA gels inhibits N-cadherin, resulting in stronger intercellular adhesion on cells on AA gels compared to cells on AM

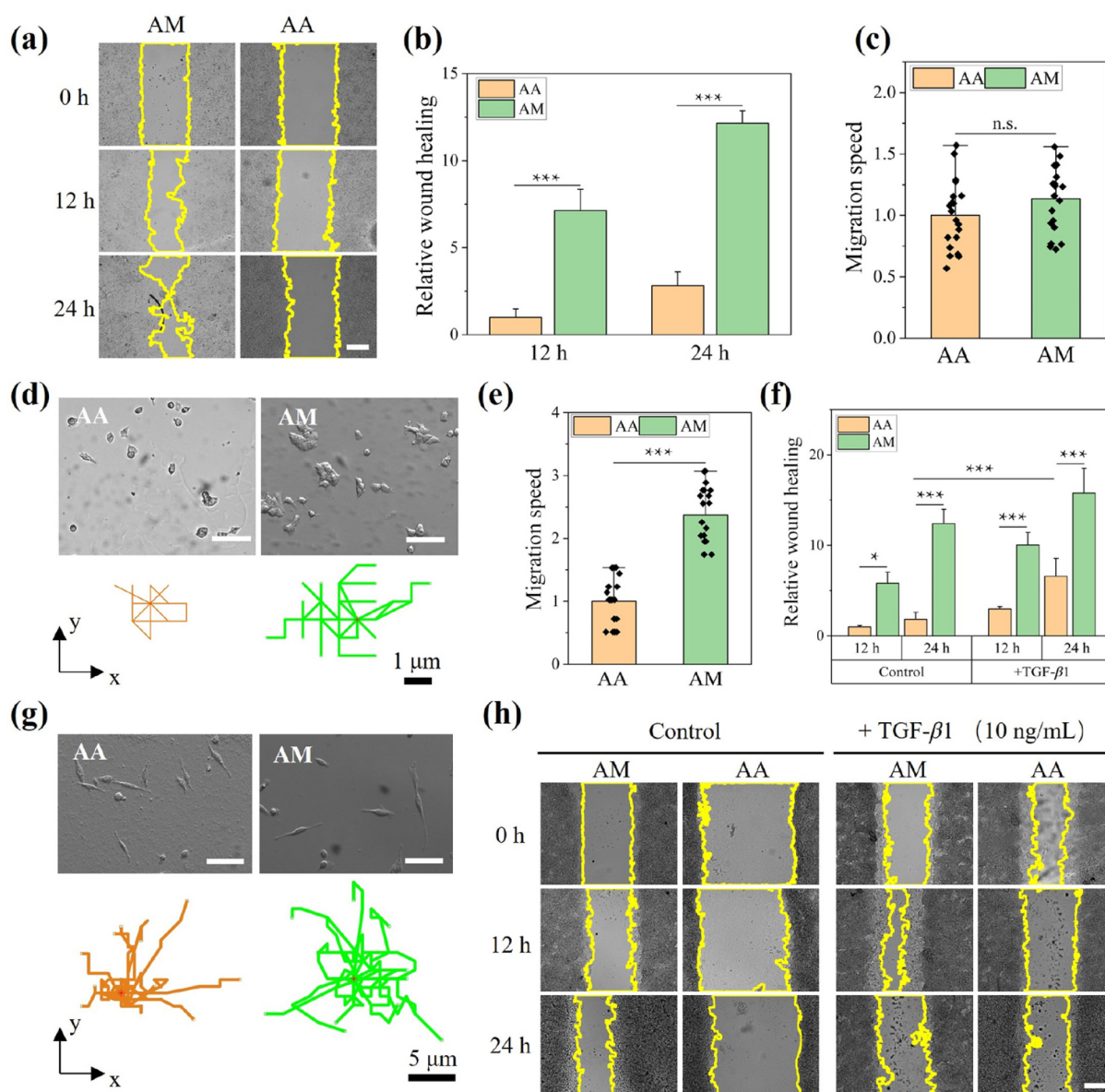


Figure 2 Migration of cells cultured on different hydrogel substrates. (a) The wound healing conditions of Huh-7 cells on AA gel and AM gel. This presented the wound closure situations at the beginning of the experiment (top), 12 h (middle), and 24 h (bottom). Scale bar: 200 μ m. (b) The rate of wound healing of Huh-7 cells corresponding to panel (a). (c) The relative movement speed of THLE-2 on AA and AM gels ($n = 20$). (d) The movement trajectories of Huh-7 on AA and AM gels within 1 h. Scale bars: 100 μ m. (e) The speed of Huh-7 cultured on AA gels and AM gels within 1 h ($n = 18$). (f) The rate of wound healing of Hep-G2 cells corresponding to panel (h). (g) The movement trajectory of THLE-2 on AA and AM gels within 1 h. Scale bars: 100 μ m. (h) Representative optical images of wound healing of Huh-7 treated without (left panel) and with transforming growth factor- β 1 (TGF- β 1) (right panel). Scale bar: 200 μ m.

gels (Fig. 3(f)). This consequently leads to reduced cellular migration, which is likely a significant factor contributing to the slower scratch recovery.

2.3 Differences in the cytoskeleton

Cell morphology is closely linked to cell migration and the spindle-shaped cell morphology can significantly promote cell migration [34]. For cells on AM gels and AA gels, experimental results revealed distinct cellular morphologies (Fig. 4(a)). Among them, the aspect ratio (the ratio of the long diagonal to the short diagonal of the cell) of cells on AA gels is significantly lower than that on AM gels (Figs. 4(a) and 4(d)), indicating that the cell morphologies on the two gels are quite different. The cells change from the cuboidal shape on the AA gel to the spindle-shaped form on the AM gel, cell

migration on AA gels was thus inhibited. Furthermore, the cell morphology here also corresponds to the changes in cell adhesion described in the previous text (Figs. 3(c) and 3(d)). This observed morphological difference was generally considered to stem from variations in the underlying cytoskeleton [35] and the maturation of focal adhesions (FAs) and F-actin assembly is the main factor causing the change in cell morphology [36, 37]. The focal adhesion plaques and microfilaments are also the important components affecting cell migration.

Consequently, we proceeded to investigate the cellular cytoskeleton. The focal adhesion plaques and microfilaments are also the important components affecting cell migration. Through experiments, we found that the microfilaments and actin proteins on the AA gel were significantly less than those on the AM

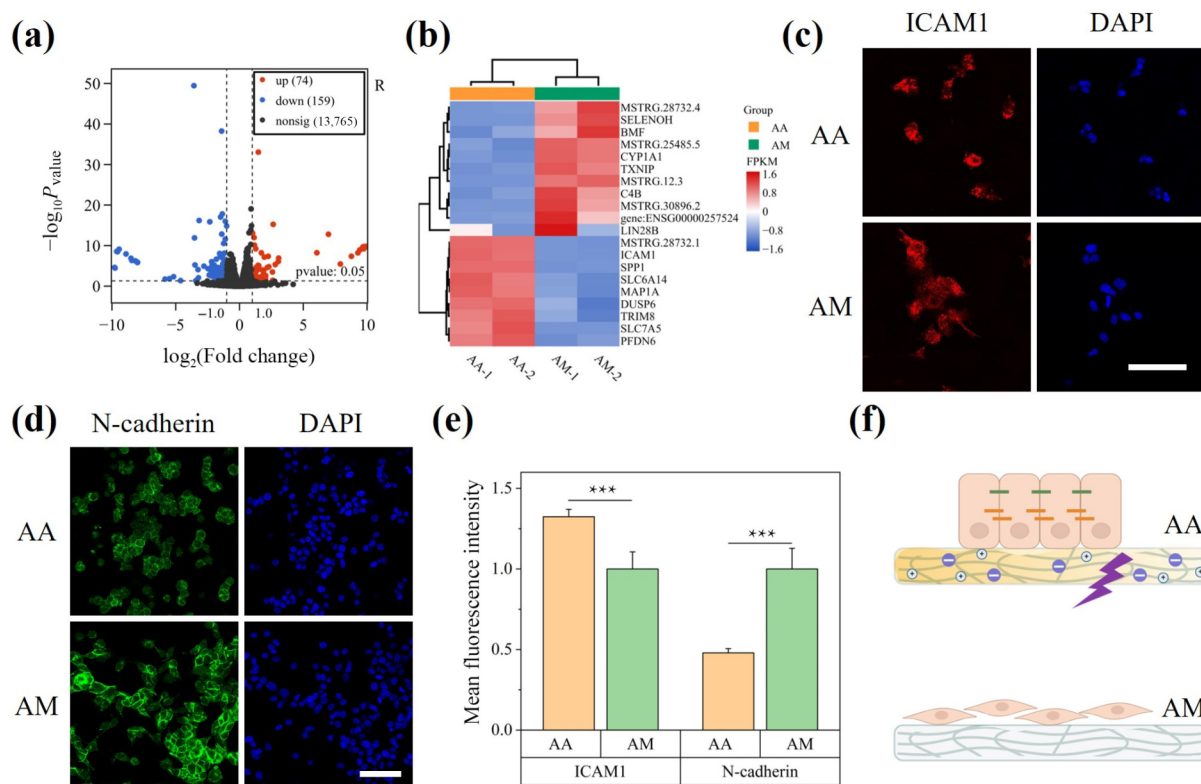


Figure 3 Integrated visualization of gene expression heatmaps and gene-set functional category counts. (a) The fold change in gene expression between the two groups. The horizontal axis represents $\log_2(\text{Fold change})$ ($\log_2\text{FC}$), while the vertical axis represents $-\log_{10}P_{\text{value}}$ reflecting the significance level of the gene expression difference. (b) A heatmap displaying the relative expression levels of selected genes across samples after Z-score normalization. Rows represent genes and columns represent samples. The color scale ranges from blue to red, denoting the minimum to maximum values, with blue indicating low expression and red indicating high expression. (c) Through fluorescence labeling, the differences in the expression of cells on the two hydrogels for ICAM1 (red). The cells on the AA gel showed more N-cadherin. Scale bar: 100 μm . (d) Cytoskeleton structure of Huh-7 cultured on AA gel and AM gel. Through fluorescence labeling, the differences in the expression of cells on the two hydrogels for N-cadherin (green). The cells on the AA gel showed less N-cadherin. Scale bar: 100 μm . (e) A quantitative representation of ICAM1 and N-cadherin on these two gels ($n = 8$). (f) The intercellular adhesion of cells on AA gels and AM gels.

gel (Fig. 4(c) and Fig. S3 in the ESM), indicating that this weak actin may be one of the reasons for the slow cell migration on the AA gel. The difference in the strength of the microfilaments and focal adhesions explains the observed disparity in single-cell migration capabilities on the two gels, and should also be a significant contributor to the slow scratch recovery. Therefore, due to the piezoelectric properties of AA gels, by inhibiting the assembly and maturation of F-actin and FAs separately, the cell morphology can be regulated and cell migration can be affected.

To further explore the mechanisms influencing cell migration, we tested the mitochondrial membrane potential of cells on the two gels. On the AA gels, there was an increase in green fluorescence (JC-1 monomers) and a decrease in red fluorescence (JC-1 aggregates) in cells compared to that on the AM gel (Fig. 4(b)). Based on these observations, it appears that the AA gel leads to a decrease in mitochondrial membrane potential compared to the AM gels. These results indicate that cells on the AA gel showed an early cell apoptosis situation, which may be related to the slower cell migration on the AA gel. It is possible that electricity generated by cells on AA gels triggered mitochondrial damage, which impaired the formation and maintenance of the cytoskeleton, thereby affecting cell migration.

The difference between AA gels and AM gels lies in whether they can undergo piezoelectric conversion. Due to the traction force exerted by the cells on the AA gel, the base will generate electricity

which will act on the cells in turn, thereby possibly affecting cell migration. Therefore, we used drugs that can influence the traction force (Fig. 4(e)). Among them, cytochalasin D (Cyto-D) is a fungal metabolite that can penetrate cells and inhibit the polymerization of actin, reducing the traction force and the migration of the cells [38], possibly thereby affecting the electricity generated by the piezoelectric hydrogel. Through experiments, we can clearly see that the cells on the AM gel (Figs. 4(e) and 4(f)), under the influence of Cyto-D, had a significantly slower migration speed; this is consistent with the effect of Cyto-D.

While the cells on the AA gel, Cyto-D can inhibit actin, but the cell migration does not decrease ("AA" in "control" in Fig. 4(f)), instead, it increases. Similarly, Y-27632 (Y27), as an inhibitor of the Rho-associated coiled-coil containing protein kinase (ROCK) signaling pathway, can inhibit myosin phosphorylation, thereby inhibiting cell migration; cell migration on AM gels was indeed inhibited. Similar to Cyto-D, the cells on the AA gels showed an improvement in migration after adding this drug (Fig. 4(f)). This observation may be attributed to the following mechanisms: In the absence of electrical stimulation, cells are generally expected to exhibit enhanced force generation and faster migratory speeds. However, in practical scenarios, the electrical stimulation provided by AA gels may elicit a feedback effect on the cells. That is, the forces generated by cells during migration activate electrical signals in AA gels which may in turn weaken the cells' force generation

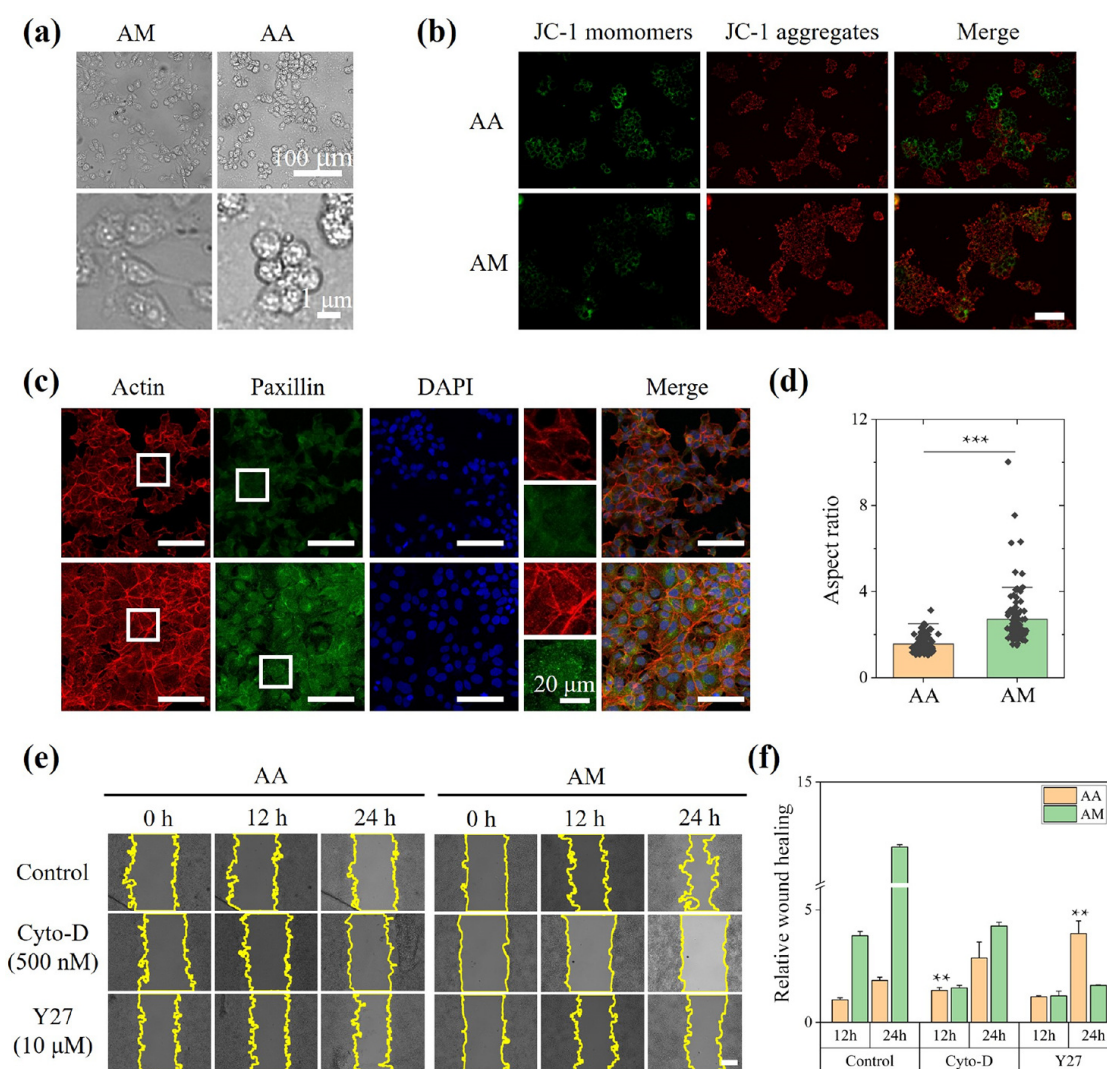


Figure 4 The growth status of cells on two types of hydrogel substrates and the migration of cells under the action of drugs. (a) The differences in cell morphology grown on AA gels and AM gels in bright-field microscopy. (b) JC-1 fluorescence staining. This was used to assess the changes in mitochondrial membrane potential. The AA group showed a significantly enhanced green signal and a lower red signal. On the contrary, the AM group exhibited a significantly enhanced red signal and a decreased green signal. The combined image showed a strong contrast between red and green. Scale bar: 200 μm. (c) Cytoskeleton structure of Huh-7 cultured on AA gels and AM gels. Through fluorescence labeling, the differences in the expression of cells on the two hydrogels for F-actin (red), and paxillin (green) were demonstrated. The cells on the AA gel showed less fibers and focal adhesions. Scale bars: 100 μm; inserted: 20 μm. (d) The statistics of the cell length-to-width ratio ($n = 100$). (e) The cell migration on the two types of hydrogels when adding the actin inhibitor (500 nM cytochalasin D, 10 μM Y-27632). Scale bar: 200 μm. (f) A quantitative representation of the migration of Huh-7 ($n = 3$).

and migration capabilities. Conversely, when cells are treated with Cyto-D (Y27), the inherent force generation and migratory capabilities are significantly compromised from the outset. This results in a very weak intrinsic electrical signal which may have a minimal impact on cellular force generation and migration. The findings presented in Fig. 4(e) further corroborate this hypothesis: at the 12 h time point, the migratory capacity of cells treated with Cyto-D (Y27) on AM gels was comparable to that observed on AA gels. This suggests that the primary determinant of cell migration ability at this stage is the inhibition of the cytoskeleton by Cyto-D (Y27), with the electrical signal induced by AA gels having a substantially reduced influence on migration. Notably, at the 24 h time point, a decrease in migratory capacity on AM gels relative to the control group ("Control" in Fig. 4(f)) was observed, while an increase in migratory capacity on AA gels relative to the control group was evident. This further supports that electrical stimulation

on AA gels has a diminished effect on cell migration under the drug treatment condition. Furthermore, it is noteworthy that upon treatment with pharmacological agents, cell migration was paradoxically enhanced. This observation further suggests that the piezoelectric hydrogel possesses a potential regulatory mechanism wherein its inhibitory effect on cell migration may be more pronounced for cells exhibiting higher migratory speeds.

2.4 Differential expression of Piezo1 and intracellular calcium ion levels

The difference between the two types of hydrogels lies in whether they have the piezoelectric effect, and the commonly used channel related to electricity is the Piezo1 channel. A moderate increase in Piezo1 will promote the influx of calcium ions (Ca^{2+}), thereby facilitating cell motility [39–42]. Therefore, we conducted an immunofluorescence experiment and found that the Piezo1 of cells

on AA gels was more than that on AM gels (Figs. 5(a) and 5(b)). We further measured the intracellular calcium ion content in the cells on the two types of hydrogels. The cells on the AA gel contained higher levels of Ca^{2+} (Figs. 5(e) and 5(f)). We hypothesized that there was a calcium overload phenomenon within the cells on the AA gel because of the activation of Piezo1,

which inhibited cell migration. To verify this assumption, firstly, we used the agonist Yoda-1 and the inhibitor GsMTX-4 of the Piezo1 to examine the speed of cell migration under different Piezo1 levels. When Yoda-1 was added, the cell migration on AM gels increased (Figs. 5(c) and 5(d)); this is consistent with the finding that cells on AM gels did not exhibit calcium overload, and promoting

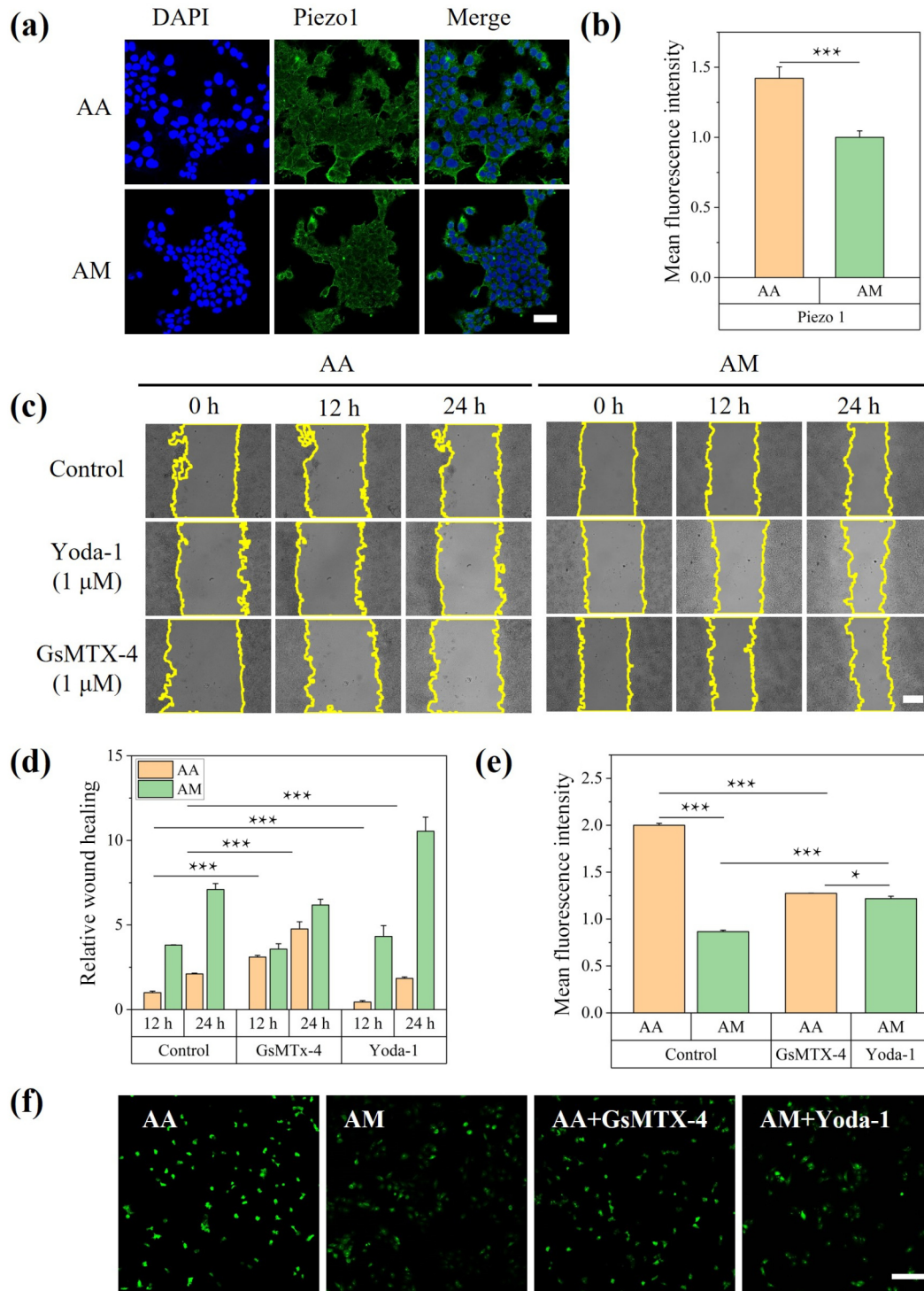


Figure 5 The expression levels of piezo1 on two types of hydrogel substrates and the migration conditions and calcium ion content of cells treated with piezo1 agonists and antagonists. (a) The fluorescence levels of piezo1 on the AA gel (top) and the AM gel (below). The cells on the AA gel showed more Piezo1. Scale bar: 100 μm . (b) A quantitative representation of Piezo1 on these two gels ($n = 10$). (c) The cell migration of Huh-7 on AA and AM gels when adding the piezo1 agonist (1 μM Yoda-1) and inhibitor (1 μM GsMTX-4). Scale bar: 200 μm . (d) A quantitative representation of panel (c) ($n = 3$). (e) A quantitative representation of panel (f) ($n = 3$). (f) The calcium ion levels of cells on AA gels, AM gels, AA gels with GsMTX-4 added (AA+GsMTX-4) and AM gel with Yoda-1 added (AM+Yoda-1), scale bar: 200 μm .

migration by activating the Piezo1 pathway to facilitate a moderate increase in Ca^{2+} . While the cell migration on AA gels was slowed down significantly. This is consistent with the fact that cells on AA gels are already calcium-overloaded, and further Ca^{2+} influx leads to even greater overload, thereby affecting their migration. Conversely, when GsMTX-4 was added, the cell migration on AM gels decreased because cells on the AM gel did not exhibit calcium overload and inhibiting Piezo1 channel opening reduced calcium ion influx, thereby slowing migration. While the cell migration on AA gels was faster (Figs. 5(c) and 5(d)), whose reason is that calcium overload occurred within the cells and then inhibiting the opening of Piezo1 channels reduces calcium ion influx, thereby mitigating the adverse effects of calcium overload. Then we tested the relative content of Ca^{2+} under different conditions. Initially, the Ca^{2+} content on the AA gel was high, while that on the AM gel was low (Figs. 5(e) and 5(f)). Upon the addition of Yoda-1, an agonist of Piezo1, intracellular Ca^{2+} levels were elevated. Conversely, when the inhibitor GsMTX-4 was introduced, intracellular Ca^{2+} levels exhibited a decrease.

For AM gels, the cells are initially in a normal state, so adding the agonist of the Piezo1 would cause the migration to speed up due to an increase in Ca^{2+} influx. Conversely, for AA gels, this phenomenon may be attributable to the enhanced activation of Piezo1 channels induced by AA gels, leading to excessive Ca^{2+} influx and subsequent cellular calcium overload. This calcium overload could further impair mitochondrial function, disrupt cytoskeletal synthesis, and inhibit cell migration [43–45].

The presence of Yoda-1 exacerbates the degree of calcium overload, thereby resulting in a significant deceleration of cell migration. However, when adding GsMTX-4, the phenomenon of calcium overload will be improved, and cell migration will accelerate. Furthermore, we conducted a cell migration experiment. When we added 1 mM Ca^{2+} to the cells on the two types of hydrogels respectively, we found that for the cells on the AM gel, adding Ca^{2+} promoted migration, however, for AA gels, the addition of Ca^{2+} inhibited the migration (Figs. 6(a) and 6(b)).

On AM gels, there is no calcium overload and the intracellular calcium levels remain within the normal range. The addition of moderate Ca^{2+} promotes cell migration by enhancing the coupling between actin cytoskeleton and adhesion complexes, thereby facilitating the efficient execution of detachment events within the dynamic adhesion-disassembly cycle and accelerating migratory speed. In contrast, on AA gels, intracellular calcium ions are in an overloaded state. The addition of Ca^{2+} inhibits migration, because further Ca^{2+} influx could exacerbate calcium toxicity, disrupting cytoskeletal synthesis, and inhibiting cell migration. To further evaluate the plausibility of the calcium-overload hypothesis, we quantified intracellular Ca^{2+} levels under various conditions. We observed that cells on AA gels exhibited significantly higher intracellular Ca^{2+} concentrations, which further increased upon the addition of external Ca^{2+} (Figs. 6(c) and 6(d)). In contrast, irrespective of whether Ca^{2+} was added, cells on AM gels maintained intracellular Ca^{2+} levels that remained consistently lower than those of the AA gel condition. These findings suggest that cells on AA gels are already in a calcium-overloaded state at baseline.

Specifically, piezoionic hydrogels induce intracellular calcium overload by activating the Piezo1 ion channel, leading to excessive calcium influx. Sustained calcium overload may impair mitochondrial function, and consequently disrupt the formation and maintenance of the cytoskeleton, ultimately hindering cell

motility (Fig. 6(e)). Furthermore, we show that a simple and cost-effective intervention that augmenting intracellular calcium ions under piezoelectric stimulation can significantly amplify this cancer cell migration inhibition.

3 Conclusions

In summary, this study, through piezoionic hydrogels, investigated the effect of force-electric stimulation on cancer cell migration. Compared to normal cells, cancer cells typically exhibit higher migratory capabilities. This study reveals that piezoionic hydrogels specifically inhibit cancer cell migration by exploiting the cells' inherent strong motility while having minimal effect on the migration of normal cells with relatively weaker motility. This approach offers advantages including simple operation, no external energy supply requirement, and the ability to deliver sustained spontaneous stimulation. Specifically, the upregulation of Piezo1 expression induced by piezoionic hydrogels and the increase in intracellular calcium ion concentration led to calcium overload, leading to a reduction in F-actin and focal adhesions, thereby decreasing cell migration. And there is a significant upregulation of cell adhesion-related genes (such as *ICAM1*) on the piezoionic hydrogel, along with a downregulation of N-cadherin expression. These alterations in the cell cytoskeleton and cell adhesion molecules synergistically inhibit cell motility. Furthermore, we show that a simple and cost-effective intervention that augmenting intracellular calcium under piezoelectric stimulation can significantly further enhance the inhibitory effect on the migration of cancer cells. These findings provide a crucial theoretical foundation for designing piezoionic hydrogels based anti-cancer strategies. Our research demonstrates that piezoionic hydrogels can specifically inhibit the migration of cancer cells, offering a novel approach for developing therapies targeting cancer cell motility.

From a broader perspective, the strategy of using piezoelectric hydrogels to inhibit cancer cell migration can be viewed as a "motility trap". By artificially constructing a microenvironment unfavorable for cancer cell movement, we can limit the spread and metastasis of cancer cells, thereby improving the effectiveness of cancer treatment without the influence of normal cells. Future research can explore how to optimize the performance of piezoionic hydrogels to inhibit cancer cell motility more effectively and combine them with other therapies (such as chemotherapy, radiotherapy) to achieve better anti-cancer outcomes.

Electronic Supplementary Material: Supplementary material (detailed experimental methods, material and biochemical characterization, more scratch experiment results, immunofluorescence imaging and single-cell migration analysis) is available in the online version of this article at <https://doi.org/10.26599/NR.2026.94908694>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 12232017 and 12222212).

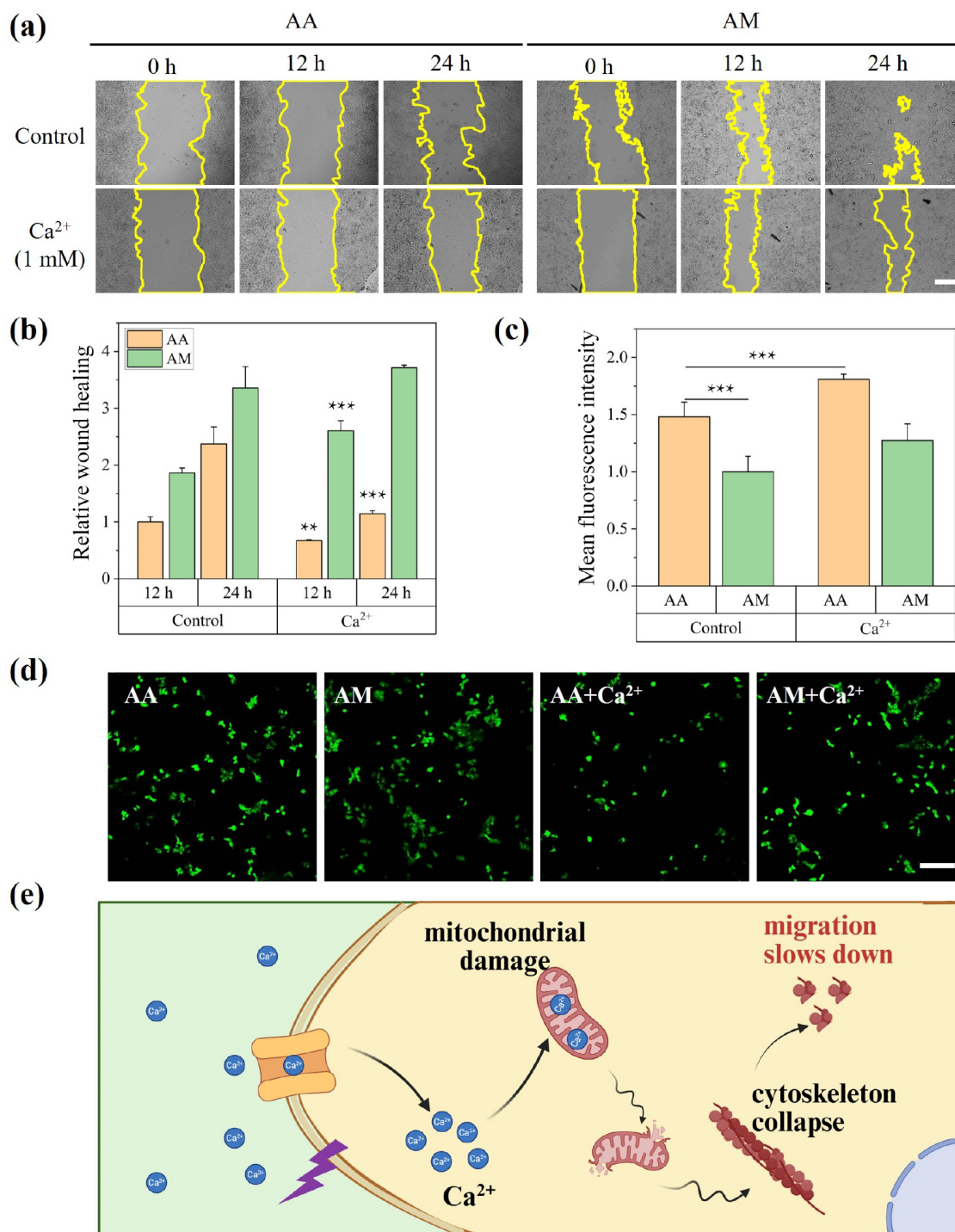


Figure 6 The migration of cells and the levels of calcium ion on two types of hydrogels substrates under the conditions of adding calcium ions. (a) Different effects on cell migration when adding 1 mM calcium ions to AA gels and AM gels. Scale bar: 200 μm . (b) A quantitative representation of panel (a). (c) A quantitative representation of panel (d) ($n = 5$). This indicated that piezo1 affects the intracellular calcium ion levels. (d) The calcium ion levels of cells on AA gels, AM gels, AA gels with Ca^{2+} added (AA+ Ca^{2+}), and AM gel with Ca^{2+} added (AM+ Ca^{2+}). Scale bar: 200 μm . (e) Schematic diagram of apoptosis mediated by piezoionic hydrogels.

Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

X. R. L.: Conceptualization, investigation, methodology,

experimental design, validation, visualization, data curation, writing manuscript. T. Z.: Experimental design, visualization. C. W.: Experimental design. Z. H. Q.: Methodology. Q. C. Z.: Supervision, funding acquisition, project administration, review & editing. S. Q. W.: Conceptualization, supervision, funding acquisition, project administration, review & editing. All the authors have approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

References

- [1] Turajlic, S.; Swanton, C. Metastasis as an evolutionary process. *Science* **2016**, *352*, 169–175.
- [2] Valastyan, S.; Weinberg, R. A. Tumor metastasis: Molecular insights and evolving paradigms. *Cell* **2011**, *147*, 275–292.
- [3] Gupta, G. P.; Massagué, J. Cancer metastasis: Building a framework. *Cell* **2006**, *127*, 679–695.
- [4] Wang, D. P.; Shen, J.; Qin, C. Y.; Li, Y. M.; Gao, L. J.; Zheng, J.; Feng, Y. L.; Yan, Z.; Zhou, X.; Cao, J. M. Platinum nanoparticles promote breast cancer cell metastasis by disrupting endothelial barrier and inducing intravasation and extravasation. *Nano Res.* **2022**, *15*, 7366–7377.
- [5] Yang, M. J.; Tang, Z. Y.; Li, X. Y.; Yu, Y. Z.; He, L. Z.; Chen, T. F. Designing macrophage membrane-engineered ruthenium/selenium nanoparticles to block bone metastasis of breast cancer. *Nano Res.* **2024**, *17*, 7504–7512.
- [6] van den Boogaard, W. M. C.; Komninos, D. S. J.; Vermeij, W. P. Chemotherapy side-effects: Not all DNA damage is equal. *Cancers* **2022**, *14*, 627.
- [7] Maduro, J. H.; Pras, E.; Willemse, P. H. B.; de Vries, E. G. E. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treat. Rev.* **2003**, *29*, 471–488.
- [8] Vijayakumar, S.; Awan, A.; Karrison, T.; Culbert, H.; Chan, S.; Kolker, J.; Low, N.; Halpern, H.; Rubin, S.; Chen, G. T. Y. et al. Acute toxicity during external-beam radiotherapy for localized prostate cancer: Comparison of different techniques. *Int. J. Radiat. Oncol. Biol. Phys.* **1993**, *25*, 359–371.
- [9] Marijnen, C. A. M.; Kapiteijn, E.; van de Velde, C. J. H.; Martijn, H.; Steup, W. H.; Wiggers, T.; Kranenbarg, E. K.; Leer, J. W. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: Report of a multicenter randomized trial. *J. Clin. Oncol.* **2002**, *20*, 817–825.
- [10] Shim, G.; Breinyn, I. B.; Martínez-Calvo, A.; Rao, S.; Cohen, D. J. Bioelectric stimulation controls tissue shape and size. *Nat. Commun.* **2024**, *15*, 2938.
- [11] Thirivikraman, G.; Boda, S. K.; Basu, B. Unraveling the mechanistic effects of electric field stimulation towards directing stem cell fate and function: A tissue engineering perspective. *Biomaterials* **2018**, *150*, 60–86.
- [12] Love, M. R.; Sripetchwandee, J.; Palee, S.; Chattipakorn, S. C.; Mower, M. M.; Chattipakorn, N. Effects of biphasic and monophasic electrical stimulation on mitochondrial dynamics, cell apoptosis, and cell proliferation. *J. Cell. Physiol.* **2019**, *234*, 816–824.
- [13] Abedin-Do, A.; Zhang, Z.; Douville, Y.; Méthot, M.; Bernatchez, J.; Rouabhia, M. Electrical stimulation promotes the wound-healing properties of diabetic human skin fibroblasts. *J. Tissue Eng. Regen. Med.* **2022**, *16*, 643–652.
- [14] Wang, M. K.; Wu, Y.; Li, G. F.; Lin, Q. S.; Zhang, W. C.; Liu, H.; Su, J. C. Articular cartilage repair biomaterials: Strategies and applications. *Mater. Today Bio* **2024**, *24*, 100948.
- [15] Ricotti, L.; Cafarelli, A.; Manferdini, C.; Trucco, D.; Vannozzi, L.; Gabusi, E.; Fontana, F.; Dolzani, P.; Saleh, Y.; Lenzi, E. et al. Ultrasound stimulation of piezoelectric nanocomposite hydrogels boosts chondrogenic differentiation *in vitro*, in both a normal and inflammatory milieu. *ACS Nano* **2024**, *18*, 2047–2065.
- [16] Wang, F.; Qiu, J. J.; Guan, S. W.; Chen, S. H.; Nie, X. S.; Fu, Z. Q.; Yao, F. Z.; Gong, W.; Wang, K.; Liu, X. Y. An ultrasound-responsive hydrogel with piezoelectric-enhanced electrokinetic effect accelerates neurovascular regeneration for diabetic wound healing. *Mater. Today* **2025**, *84*, 48–64.
- [17] Luo, J. L.; Liang, Z.; Zhao, X.; Huang, S. F.; Gu, Y. N.; Deng, Z. X.; Ye, J.; Cai, X. M.; Han, Y.; Guo, B. L. Piezoelectric dual-network tough hydrogel with on-demand thermal contraction and sonopiezoelectric effect for promoting infected-joint-skin-wound healing via FAK and AKT signaling pathways. *Natl. Sci. Rev.* **2025**, *12*, nwaf118.
- [18] Roca-Cusachs, P.; Conte, V.; Trepát, X. Quantifying forces in cell biology. *Nat. Cell Biol.* **2017**, *19*, 742–751.
- [19] Polacheck, W. J.; Chen, C. S. Measuring cell-generated forces: A guide to the available tools. *Nat. Methods* **2016**, *13*, 415–423.
- [20] Tan, J. L.; Tien, J.; Pirone, D. M.; Gray, D. S.; Bhadriraju, K.; Chen, C. S. Cells lying on a bed of microneedles: An approach to isolate mechanical force. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 1484–1489.
- [21] Chorsi, M. T.; Curry, E. J.; Chorsi, H. T.; Das, R.; Baroody, J.; Purohit, P. K.; Ilies, H.; Nguyen, T. D. Piezoelectric biomaterials for sensors and actuators. *Adv. Mater.* **2019**, *31*, 1802084.
- [22] Hoop, M.; Chen, X. Z.; Ferrari, A.; Mushtaq, F.; Ghazaryan, G.; Tervoort, T.; Poulikakos, D.; Nelson, B.; Pané, S. Ultrasound-mediated piezoelectric differentiation of neuron-like PC12 cells on PVDF membranes. *Sci. Rep.* **2017**, *7*, 4028.
- [23] Genchi, G. G.; Ceseracciu, L.; Marino, A.; Labardi, M.; Marras, S.; Pignatelli, F.; Bruschini, L.; Mattoli, V.; Ciofani, G. P(VDF-TrFE)/BaTiO₃ nanoparticle composite films mediate piezoelectric stimulation and promote differentiation of SH-SY5Y neuroblastoma cells. *Adv. Healthcare Mater.* **2016**, *5*, 1808–1820.
- [24] Sarwar, M. S.; Dobashi, Y.; Preston, C.; Wyss, J. K. M.; Mirabbasi, S.; Madden, J. D. W. Bend, stretch, and touch: Locating a finger on an actively deformed transparent sensor array. *Sci. Adv.* **2017**, *3*, e1602200.
- [25] Dobashi, Y.; Yao, D.; Petel, Y.; Nguyen, T. N.; Sarwar, M. S.; Thabet, Y.; Ng, C. L. W.; Scabeni Glitz, E.; Nguyen, G. T. M.; Plesse, C. et al. Piezoionic mechanoreceptors: Force-induced current generation in hydrogels. *Science* **2022**, *376*, 502–507.
- [26] Ghosh, K.; Thodeti, C. K.; Dudley, A. C.; Mammoto, A.; Klagsbrun, M.; Ingber, D. E. Tumor-derived endothelial cells exhibit aberrant Rho-mediated mechanosensing and abnormal angiogenesis *in vitro*. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 11305–11310.
- [27] Shiraishi, T.; Verdone, J. E.; Huang, J.; Kahlert, U. D.; Hernandez, J. R.; Torga, G.; Zarif, J. C.; Epstein, T.; Gatenby, R.; McCartney, A. et al. Glycolysis is the primary bioenergetic pathway for cell motility and cytoskeletal remodeling in human prostate and breast cancer cells. *Oncotarget* **2015**, *6*, 130–143.
- [28] Kraning-Rush, C. M.; Califano, J. P.; Reinhart-King, C. A. Cellular traction stresses increase with increasing metastatic potential. *PLoS One* **2012**, *7*, e32572.
- [29] Wang, C.; Zhao, X. Y.; Yan, T. H.; Zhang, S. X.; Li, X. R.; Chen, Y.; Wu, W. J.; Qiao, Z. H.; Chen, Q. B.; Wang, X. W. et al. High efficiency production of functional small extracellular vesicles through cellular self-motivation. *Nano Lett.* **2025**, *25*, 6471–6480.
- [30] Nieto, M. A.; Huang, R. Y. J.; Jackson, R. A.; Thiery, J. P. EMT: *Cell* **2016**, *166*, 21–45.
- [31] Hong, E.; Brewster, R. *N-cadherin* is required for the polarized cell behaviors that drive neurulation in the zebrafish. *Development* **2006**, *133*, 3895–3905.
- [32] Wan, S. S.; Wang, K. P.; Huang, P. H.; Guo, X.; Liu, W. R.; Li, Y. C.; Zhang, J. J.; Li, Z. Y.; Song, J. C.; Yang, W. J. et al. Mechano-electronic stimulation of autologous extracellular vesicle

- biosynthesis implant for gut microbiota modulation. *Nat. Commun.* **2024**, *15*, 3343.
- [33] Hazan, R. B.; Phillips, G. R.; Qiao, R. F.; Norton, L.; Aaronson, S. A. Exogenous expression of N-cadherin in breast cancer cells induces cell migration, invasion, and metastasis. *J. Cell Biol.* **2000**, *148*, 779–790.
- [34] Yang, B. L.; Zhu, P.; Li, Y. R.; Xu, M. M.; Wang, H.; Qiao, L. C.; Xu, H. X.; Chen, H. J. Total flavone of *Abelmoschus manihot* suppresses epithelial-mesenchymal transition via interfering transforming growth factor- β 1 signaling in Crohn's disease intestinal fibrosis. *World J. Gastroenterol.* **2018**, *24*, 3414–3425.
- [35] Fletcher, D. A.; Mullins, R. D. Cell mechanics and the cytoskeleton. *Nature* **2010**, *463*, 485–492.
- [36] Massou, S.; Nunes Vicente, F.; Wetzel, F.; Mehidi, A.; Strehle, D.; Leduc, C.; Voituriez, R.; Rossier, O.; Nassoy, P.; Giannone, G. Cell stretching is amplified by active actin remodelling to deform and recruit proteins in mechanosensitive structures. *Nat. Cell Biol.* **2020**, *22*, 1011–1023.
- [37] Kakinoki, S.; Seo, J. H.; Inoue, Y.; Ishihara, K.; Yui, N.; Yamaoka, T. Mobility of the Arg-Gly-Asp ligand on the outermost surface of biomaterials suppresses integrin-mediated mechanotransduction and subsequent cell functions. *Acta Biomater.* **2015**, *13*, 42–51.
- [38] Gil-Redondo, J. C.; Weber, A.; Vivanco, M. D.; Toca-Herrera, J. L. Measuring (biological) materials mechanics with atomic force microscopy. 5. Traction force microscopy (cell traction forces). *Microsc. Res. Tech.* **2023**, *86*, 1069–1078.
- [39] Atcha, H.; Jairaman, A.; Holt, J. R.; Meli, V. S.; Nagalla, R. R.; Veerasubramanian, P. K.; Brumm, K. T.; Lim, H. E.; Othy, S.; Cahalan, M. D. et al. Mechanically activated ion channel Piezo1 modulates macrophage polarization and stiffness sensing. *Nat. Commun.* **2021**, *12*, 3256.
- [40] Déliot, N.; Constantin, B. Plasma membrane calcium channels in cancer: Alterations and consequences for cell proliferation and migration. *Biochim. Biophys. Acta (BBA) - Biomembr.* **2015**, *1848*, 2512–2522.
- [41] Tsai, F. C.; Kuo, G. H.; Chang, S. W.; Tsai, P. J. Ca^{2+} signaling in cytoskeletal reorganization, cell migration, and cancer metastasis. *BioMed Res. Int.* **2015**, *2015*, 409245.
- [42] Tadge, T.; Patewar, A.; More, N.; Babu, S. S.; Velyutham, R.; Kapusetti, G. The role of Piezo1 and Piezo2 proteins in tissue engineering: A comprehensive review. *Eng. Regener.* **2024**, *5*, 170–185.
- [43] Zhang, H. D.; Yang, T. F.; Mu, W. Y.; Peng, X. H.; Liu, T.; Weng, L.; Wang, H. Y.; Zhang, Y. M.; Chen, X. Effective amplification of oxidative stress and calcium manipulation mediated mitochondrial dysfunction based on engineered nanozyme for primary and metastatic breast cancer therapy. *Small* **2025**, *21*, 2411299.
- [44] Li, J.; Ding, B. B.; Zheng, P.; Meng, Q.; Chen, H.; Tan, J.; Zhang, W. Y.; Ma, X. Y.; Zhang, J. S.; Ma, P. A. et al. Construction of diverse calcium-based nanomaterials through a microemulsion method for pyroptosis-initiated antitumor immunotherapy. *Adv. Mater.* **2026**, *38*, e16225.
- [45] He, J. N.; Wang, Y. Z.; Ren, Y. X.; Yuan, Q.; Zhang, Z. Q.; Li, L.; Bao, B. K.; Jia, W. H.; Zhang, X. Y.; Li, M. Q. et al. Calcium-mediated cell adhesion enhancement-based antimetastasis and synergistic antitumor therapy by conjugated polymer-calcium composite nanoparticles. *ACS Nano* **2024**, *18*, 24953–24967.



This is an open access article under the terms of the Creative Commons Attribution 4.0 International License (CC BY 4.0, <https://creativecommons.org/licenses/by/4.0/>).

© The Author(s) 2026. Published by Tsinghua University Press.