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Mechano-growth factor induces migration of rat mesenchymal stem cells by altering its mechanical properties and activating ERK pathway

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ABSTRACT

Mechano-growth factor (MGF) generated by cells in response to mechanical stimulation has been identified as a mechano effector molecule, playing a key role in regulating mesenchymal stem cell (MSC) function, including proliferation and migration. However, the mechanism(s) underlying how MGF-induced MSC migration occurs is still unclear. In the present study, MGF motivated migration of rat MSCs (rMSCs) in a concentration-dependent manner and optimal concentration of MGF at 50 ng/mL (defined as MGF treatment in this paper) was demonstrated. Notably, enhancement of mechanical properties that is pertinent to cell migration, such as cell traction force and cell stiffness were found to respond to MGF treatment. Furthermore, MGF increased phosphorylation of extracellular signal-regulated kinase (ERK), ERK inhibitor (i.e., PD98059) suppressed ERK phosphorylation, and abolished MGF-induced rMSC migration were found, demonstrating that ERK is involved molecule for MGF-induced rMSC migration. These in vitro evidences of MGF-induced rMSC migration and its direct link to altering rMSC mechanics and activating the ERK pathway, uncover the underlying biomechanical and biological mechanisms of MGF-induced rMSC migration, which may help find MGF-based application of MSC in clinical therapeutics.

1. Introduction

Mesenchymal stem cells (MSCs) are characterized by the ability of self-renewal and differentiation into multiple cell types, which is definitely advantageous in tissue repair and regeneration [1]. Promising fields of application with MSCs in tissue engineering cover cardiovascular repair, treatment of lung fibrosis, and bone or cartilage repair, however, the gains are meagre. These marginal gains are generally attributed to the lack of MSCs differentiation, and what's more important is poor homing of MSCs [2,3], which is characterized by MSCs migration. Enhancing the efficiency of MSC migration will raise its application in clinical therapy and regenerative medicine. Thus, a full investigation of the underlying mechanism(s) of MSCs migration is required to increase the quantity of migrated MSC in the areas of tissue damage.

Previously, a number of growth factors have been shown to enhance the clinical outcome of MSCs application by inducing MSCs' proliferation, directed differentiation and migration. In the present study, a growth factor of interest, mechano-growth factor (MGF), was observed for its role in affecting rat MSCs' (rMSCs) migration. In previous studies, MGF has been illuminated for inducing the migration of muscle stem cells and human MSCs [4], however, the underlying mechanism is not fully understood. Mechanical stimulation is known for mediating MSCs' function, like when using mechanical stretch to promote MSCs' proliferation and directed differentiation [5,6], and low shear stress to induce human MSCs migration [7]. Considering that mechano-growth factor (MGF) is a mechano effector molecule, it is possible that MGF may affect the cells' mechanics in response to mechanical stimulation, and functions similar to mechanical stimulation to induce the migration of MSCs.

Previously, extracellular signal-regulated kinase (ERK), one member of the mitogen-activated protein kinase (MAPK) pathway [8], could be activated by an extracellular signal to mediate biological cell activities, such as proliferation and migration [9]. Subsequently, activating the ERK signaling pathway involved with the migration of MSCs, and inhibiting ERK signaling by using PD98059, inhibitor of the ERK pathway, has been shown to abolish the migration of MSCs [10]. Considering that MGF can induce the migration of human MSCs, it is feasible that the ERK pathway is also involved in MGF-induced MSCs migration.

To test these hypotheses, Sprague Dawley rats bone marrow-derived MSCs (rMSCs) were isolated and cultured in vitro. The

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effect of MGF on migration of rMSCs was measured, in conjunction with changes to the mechanical properties of rMSCs. These include cell traction force, cell stiffness and the activation of ERK 1/2 pathway, elucidating the relative biomechanical and biological mechanisms of MGF-induced rMSCs migration. The results demonstrated that compared with control, MGF significantly increases the migration of rMSCs in a concentration-dependent fashion, peaking at 50 ng/mL then gradually declining with the concentration increasing. Notably, the majority of cell mechanical properties, including traction force generation and cell stiffness, appear to change in a similar manner in response to MGF stimulation. The ERK 1/2 signaling pathway was also activated in response to MGF stimulation. These imply that MGF may play a role, at least in part, in directly activating the ERK 1/2 pathway and further alter the mechanical properties of rMSCs to induce the migration of rMSCs, which uncovers underlying mechanisms of MGF-induced rMSCs migration.

2. Materials and methods

2.1. Cell isolation and culture

rMSCs were isolated by Percoll density gradient centrifugation method, as described previously [5]. Briefly, femur and tibia from Sprague–Dawley rats were sawn and gelatinous marrow was extracted under sterile conditions. rMSCs were isolated by density gradient centrifugation using Percoll (Sigma–Aldrich, Saint Louis, MO, USA d = 1.037 g/mL) for 30 min at 2500 rpm. Then rMSCs were enriched in the intermediate zone, and were cultured in Dulbecco's modification of Eagle's medium (DMEM) with 10% fetal bovine serum (FBS), penicillin (100 U/mL), streptomycin (100 μg/mL), and in 37 °C, 5% CO2 incubator. In this study, all the cells used were between passages 2–5.

2.2. Assessment of rMSC migration

Cell migration was assessed by Boyden chamber assay with 24-well Transwell (Corning, Inc., NY, USA), which has polycarbonate filters (6.5 mm diameter, 8.0 μm pore size) in the bottom as described previously [4,11]. Briefly, rMSCs were cultured in serum-free DMEM for 12 h, harvested and resuspended in DMEM with 1% FBS, then with 1×10^4 cells in 200 μL, seeded in the upper chamber with or without various concentrations MGF (Phoenix Pharmceuticals, Burlingame, CA, USA), and 600 μL DMEM containing 1% FBS in the lower chamber. For the inhibition experiment, rMSCs were resuspended and preincubated with MEK1/2 inhibitor PD98059 (50 μM, Sigma–Aldrich, Saint Louis, MO, USA) for 30 min and subsequently seeded with MGF (50 ng/mL). Cells were incubated at 37 °C and 5% CO_2 for 12 h. Then rMSCs on the upper face of the membranes were scraped using a cotton swab and those that migrated to the lower face of the membrane were fixed and stained with crystal violet in methanol. Then, migrated cells were counted in five random fields under an invert microscopy. Each group was repeated five times.

2.3. Assessment of traction force generation by rMSCs

Traction force of rMSCs was measured using Fourier Transform Traction Microscopy (FTTM), as previously described [12]. Briefly, polyacrylamide gel substrate was prepared by adjusting the ratio of 40% acrylamide and 2% bis-acrylamide to make the gel with Young's modulus at 4 kPa, embedding with fluorescence beads (diameter, 0.2 μm; F8811, Invitrogen Life Technologies, Carlsbad, CA, USA). The formed elastic substrate with diameter and thickness approximately 18 and 0.1 mm, respectively, was prepared in 35 mm cell culture dish. After gel polymerization, the elastic gel substrate was activated by sulfo-SANPAH (Pierce Biotechnology, Inc., Rockford, IL, USA), and then coated with 0.2 mg/mL collagen solution (type I, Sigma–Aldrich) overnight at 4 °C.

In order to measure traction force, cells were seeded on the elastic gel substrate at a density of ~5000 cells/well, after cells adhered and spread, they were cultured in serum-free medium with or without MGF (50 ng/mL) for 0, 6, 12 and 24 h (0 h as control). Then a single rMSC was imaged in phase contrast. Embedded fluorescence beads were also imaged in fluorescence by invert fluorescence microscopy (Leica DMI 6000B, Leica Microsystems CMS GmbH, Wetzlar, Germany) before and after cell detachment. Then net contractile moment computed by the displacement of embedded fluorescence beads measured before and after cell detachment was equivalent to the cell traction force generated by single cell [12].

2.4. Assessment of rMSC stiffness

To assess the mechanical properties of rMSCs, cell stiffness was measured by using Optical Magnetic Twisting Cytometry (OMTC), as described previously [13]. Briefly, rMSCs were seeded into a collagen (type I) coated 96-well dish (Costar, Corning, Inc., NY, USA) at a density of ~15,000 cells/well, then cultured in serum-free medium with or without MGF (50 ng/mL) for 0, 6, 12 and 24 h (0 h as control). Then, ferrimagnetic beads (diameter 4.5 μm) pre-coated with synthetic Arginine-Glycine-Aspartic Acid (RGD, Integra Life Sciences, Plainsboro Township, NJ, USA; 50 μg peptide/mg beads) were added and incubated for ~30 min in 37 °C for binding specifically to integrin receptors on the cell surface. Then beads were magnetized horizontally and twisted vertically. The cell stiffness (G') was computed from the ratio between the applied mechanical torque and later beads displacement, with the units of Pa/nm. Typically, the stiffness of rMSCs was measured at a constant oscillation frequency of 0.3 Hz for 2 min, and measured with multiple frequencies, ranging from 0.1 to 100 Hz to characterize the dynamic behavior of the cells [13].

2.5. Fluorescence staining of rMSC cytoskeleton structure

To assess the cytoskeleton structure, rMSCs were labeled with fluorescent F-actin probes. First, the rMSCs were fixed with 4% formaldehyde for 30 min after treated with or without MGF (50 ng/mL) for 0, 6, 12, 24 h (0 h as control). Then fixed cells were permeabilized with 0.2% triton X-100 in PBS for 5 min, and then stained with FITC-Phalloidin (5 μg/mL, Cytoskeleton) for 30 min. The stained cells were subsequently visualized and imaged by confocal microscope (Leica TCS SP5 II, Germany). The fluorescence intensity of F-actin in each cell was analyzed using software (Image Pro-Plus, Mediacy, Inc., Rockville, MD, USA).

2.6. Western blot

When cells grew to 80% confluent, they were treated with or without MGF (50 ng/mL) for 1 h, and for the inhibition experiment, cells were pre-treated with PD98059 for 30 min, followed by stimulation with MGF for another 1 h (in medium containing MGF and PD98059). Then cells were washed with ice-cold PBS and then lysed in ice-cold RIPA buffer supplemented with protease inhibitor cocktail (Roche, South San Francisco, CA, USA) to extract total proteins. Subsequently, equal volume of proteins solution from each group was loaded into 10% SDS–polyacrylamide gel electrophoresis, together with β-actin as loading control [11]. Proteins were transferred to PVDF membranes (Millipore, USA) and blocked with 5% non-fat milk before incubated with primary antibody overnight at 4 °C followed by incubation with corresponding horseradish

peroxidase-conjugated secondary antibodies (Wuhan Boster, Biological Technology, Ltd., Wuhan, China). Primary antibodies: rabbit anti-rat phospho-ERK 1/2, rabbit anti-rat ERK 1/2, and mouse anti-rat β-actin were purchased from Cell Signaling Technology (MA, USA) and at 1:1000. Protein expression was visualized by using an enhanced chemiluminescence kit (Beyotime Biotech, Jiangsu, China), and the ratio of the protein expression of pERK 1/2 normalized to that of tERK 1/2 was used for quantitative assessment.

2.7. Statistical analysis

All values were expressed as mean ± SD. The data of each group were analyzed by one-way analysis of variance (ANOVA) followed by *t*-test for significant differences between two groups. A level of $p < 0.05$ was accepted as statistically significant.

3. Results

3.1. MGF induced rMSC migration in a concentration-dependent manner

Fig. 1 demonstrates the effect of MGF on the migration of rMSCs as a concentration-dependent manner. Fig. 1A shows the representative images of crystal violet labeled rMSCs migrated to the bottom of transwell insert, showing 0, 10, 30, 50, 100 ng/mL, respectively (from left to right, 0 ng/mL as control). Fig. 1B shows the quantitative cell number counted by invert microscopy at the bottom of transwell, corresponding to the images showed in Fig. 1A. It can be seen that migration of rMSCs was significantly increased in all case of MGF treatment ($p < 0.001$) compared with the 0 ng/mL (control), peaked at 50 ng/mL and then gradually declined as MGF concentration increased.

3.2. MGF increased traction force of rMSC

Fig. 2 demonstrates the traction force generated by rMSCs treated either with or without MGF (50 ng/mL) for 0, 6, 12 and 24 h, as measured by FTTM. Fig. 2A, B shows the phase-contract image and the computed field of cell traction force of single rMSC cultured in elastic gel substrate, respectively. Net contractile moment (Fig. 2C) of each rMSC was quantified from the traction force field. In Fig. 2C, it was observed that compared with 0 h (control), the traction force generated by single rMSC was increased in all case of MGF (50 ng/mL) treatment. The increase was especially, significant when the cell was cultured with MGF for 6 and 12 h ($p < 0.05$, $p < 0.001$, respectively), and slightly, but not significantly, decreased for the longer of MGF treatment.

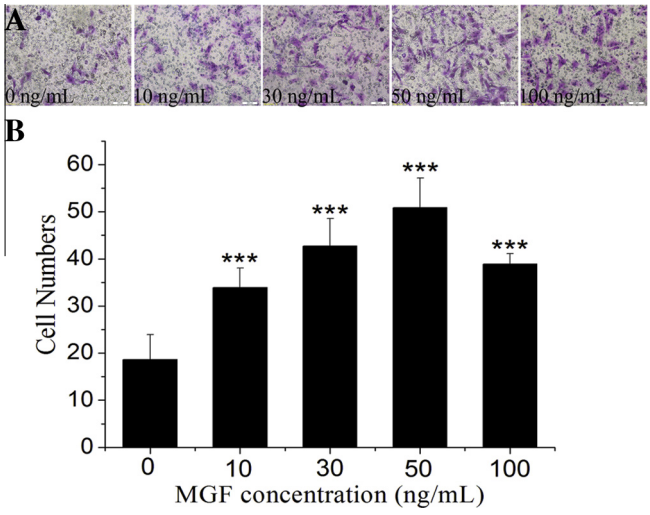

Fig. 1. MGF increased the migration of rMSCs in a concentration-dependent fashion. (A) Representative images of rMSCs migrated to the bottom of the wells treated either with or without MGF (from left to right, 0, 10, 30, 50 and 100 ng/mL, respectively). (B) The quantitative cell number of rMSCs corresponding to the images shown in (A). The result shows that MGF significantly increased rMSC migration in all case of MGF treatment, and optimal at 50 ng/mL. (***$p<0.001$, $n = 5$).

3.3. MGF caused rMSCs stiffer

Fig. 3 demonstrates the cell stiffness and cytoskeleton structure of rMSCs treated either with or without MGF (50 ng/mL) for 0, 6, 12 and 24 h, as measured by OMTC. Fig. 3A shows the cell stiffness measured at single constant frequency (0.3 Hz). Compared with the 0 h (control), G_0 of rMSCs treated with MGF increased in all cases, peaked at 12 h ($p < 0.001$), and then slightly decreased at 24 h, the change trend was similar to that of traction force generated by single rMSC. This trend was further demonstrated by cell stiffness measured against multiple-frequency. Fig. 3B shows the log–log plot of rMSCs stiffness (G') measured over the frequency of measurement (0.1–100 Hz). In all cases, the cell stiffness value increased with frequency (f) as typical power-law function ($G' \sim f^{\alpha}$), where α is between 0.1 and 0.3 for living cells [14]. It is found that cell stiffness was in ascending order of 0, 24, 6 and 12 h, and α also increased in the same trend. Cell mechanical properties are characterized by the structure and expression level of cytoskeletal protein (F-actin). Fig. 3C demonstrates the representative fluorescent images of F-actin labeled by FITC-Phalloidin and visualized by laser scanning confocal microscopy. Fig. 3D shows the mean fluorescence intensity of F-actin through analyzing the fluorescence images. It seems that MGF increased the expression of F-actin in rMSC, in particular, the increase is significant when the cell was treated for 12 h ($p < 0.05$).

3.4. ERK 1/2 was involved in MGF-induced rMSC migration

To determine whether ERK 1/2 signaling pathway is involved in MGF-induced rMSCs migration, activation of ERK 1/2 in response to MGF (50 ng/mL) was detected. Fig. 4A upper panel shows the western blot image of tERK 1/2 and pERK 1/2 from each group cells. It is found that MGF significantly increased the ERK 1/2 phosphorylation ($p < 0.001$) and MEK 1/2-specific inhibitor PD98059 restrained the effect of MGF to the base-line as control ($p < 0.001$), blocking the activation of ERK 1/2 by PD98059 significantly inhibited MGF-induced rMSCs migration, as shown in Fig. 4B ($p < 0.001$), which directly demonstrates that the ERK 1/2 signaling pathway is involved in MGF-induced rMSCs migration.

4. Discussion

The primary founding of this study was that MGF increased the migration of rMSCs in a concentration-dependent manner by altering the mechanical properties of rMSCs, and activating ERK 1/2 signaling pathway, which uncovered the underlying mechanisms of MGF-induced rMSCs migration. The effect of MGF on the migration of rMSCs peaked at 50 ng/mL, and then slightly decreased as MGF concentration increased. Notably, the majority of mechanical properties of rMSCs, including cell traction and cell stiffness, together with ERK 1/2 signaling pathway were altered and activated in response to MGF (50 ng/mL) treatment, demonstrating that cell mechanics and ERK 1/2 signaling pathway were involved in MGF-induced rMSCs migration. Considering the fact that ERK 1/2 pathway is involved in the rMSCs mechanics [15], the results imply that MGF may directly activate ERK 1/2 pathway, then regulate the

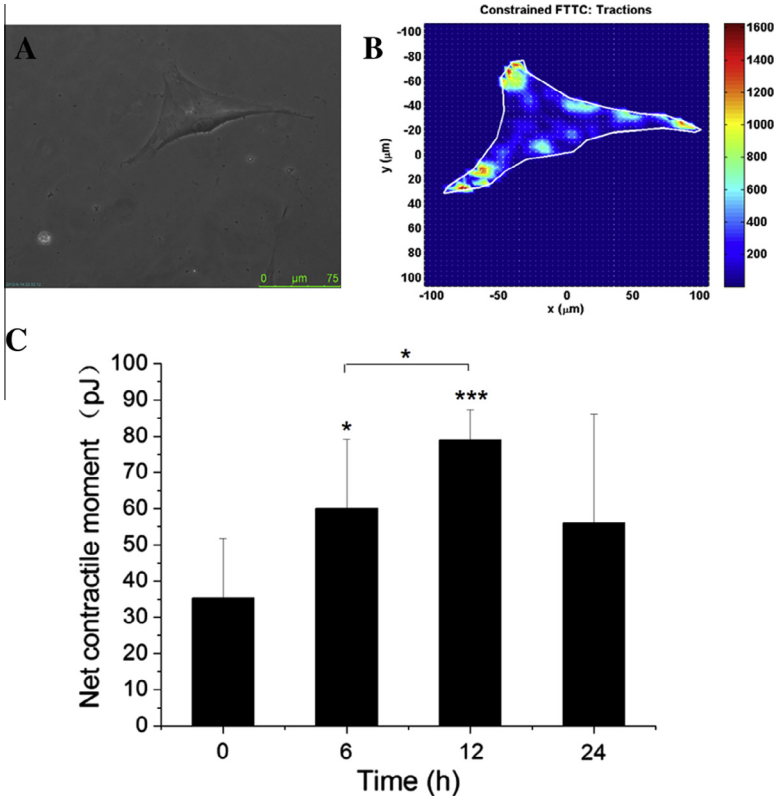

Fig. 2. Traction force generated by rMSCs treated either with or without MGF (50 ng/mL). (A) Phase-contract image of representative single rMSC cultured in polyacrylamide gel substrate. (B) Cell traction map of the corresponding cell shown in (A) measured by Fourier Transform Traction Microscopy. (C) Net contractile moment computed from the traction force map. The data bars from left to right represent the quantified net contractile moments of rMSCs treated either with or without MGF for 0 (control), 6, 12 and 24 h, respectively. The result shows that MGF significantly increased the traction force generated by rMSCs compared with control (0 h). ($^{*}p < 0.05$, $^{***}p < 0.001$, respectively, $n = 10$).

rMSCs mechanics to induce the migration of rMSCs, which uncover the biomechanical and biological mechanisms of MGF-induced rMSCs migration.

Consistent with previous studies, the concentration-dependent relation of MGF-induced rMSCs migration found in this study is similar to that of MGF-E-induced human MSCs (mesenchymal stem cells) and MPCs (myogenic precursor cells) migration illuminated previous study [4,16], showing as that the increase of migrated rMSCs number is positive with that of MGF concentration, however, the optimal concentration of MGF is different in previous and present study (30 and 50 ng/mL, respectively) [4,16]. The concentration spectrum of MGF used in previous studies is less than that used in the present study (0, 10, 30 and 100 ng/mL vs 0, 10, 30, 50 and 100 ng/mL), so the effect of 30 and 50 ng/mL MGF on hMSCs migration can not be compared. Mills et al. studied the effect of MGF on the migration of hMPCs which uses different cell type than the present study. It may be important to investigate the optimal MGF concentration to induce MSCs migration, which can better direct the application of MSCs and MGF in clinical therapy, but it is beyond the focus of this study.

Considering cell migration is a physically integrated process, it is important to uncover the underlying biomechanical mechanism [17]. Cell mechanics correlated with cell migration is confirmed in other cell types [18], thus it is feasible that MGF-induced rMSCs migration is also correlated with altering mechanical properties of rMSCs. In the present study, the majority of mechanical properties of rMSCs, including cell traction force, cell stiffness and fluidization, are shown to be positively correlated to MGF (50 ng/mL) in a time-dependent manner. Traction force is the force that an adherent cell exerts to the underlying substrate and can be balanced by the internal stress (prestress) in the cell body [19], which can help characterize cell migration capability. The experimental results demonstrate that the magnitude of traction force generated by rMSCs in all cases of MGF treatment was enhanced. The enhancement of cell traction force generated by rMSCs in response to MGF could be ascribed to a variety of factors, but not limited to the interaction of actin filaments with myosin-II (a cellular motor protein) and strengthened cytoskeletal structure [20], transmitted to the extra cellular matrix by cytoskeleton via focus adhesion [19]. All these factors would induce cells to exert greater traction force to the extra cellular matrix, and then further induce cell migration.

It is reported previously that cell tensile stress is strongly associated with cell stiffness in cytoskeleton [19]. In this study, the pattern of rMSC stiffness in response to MGF (50 ng/mL) treatment is shown to be similar to that of cell traction force, demonstrating that the magnitude of rMSCs traction force and stiffness response to MGF treatment is time-dependent, and the fluorescence intensity of cytoskeletal protein (i.e., F-actin) of MGF treated MSCs was higher compared to controls in the same time-dependent manner. Meanwhile, rMSC stiffness displayed a typical power-law behavior over a range of frequencies, which was consistent with previous studies as measured in other cell types [21]. And the slope of the power-law regression, shown as α, increased in all cases of cells treated by MGF, which means that MGF treatment enhanced the fluidization of rMSCs, suggesting the dynamic of cytoskeleton proteins is more activated and the trend of cytoskeleton remodeling is greater. All these changes in cell mechanics, either separately or all together, would enhance the physical link between rMSCs cytoskeleton and the substrate; exerting more force to induce rMSCs migration, which uncovers a biomechanical mechanism of MGF-induced rMSCs migration.

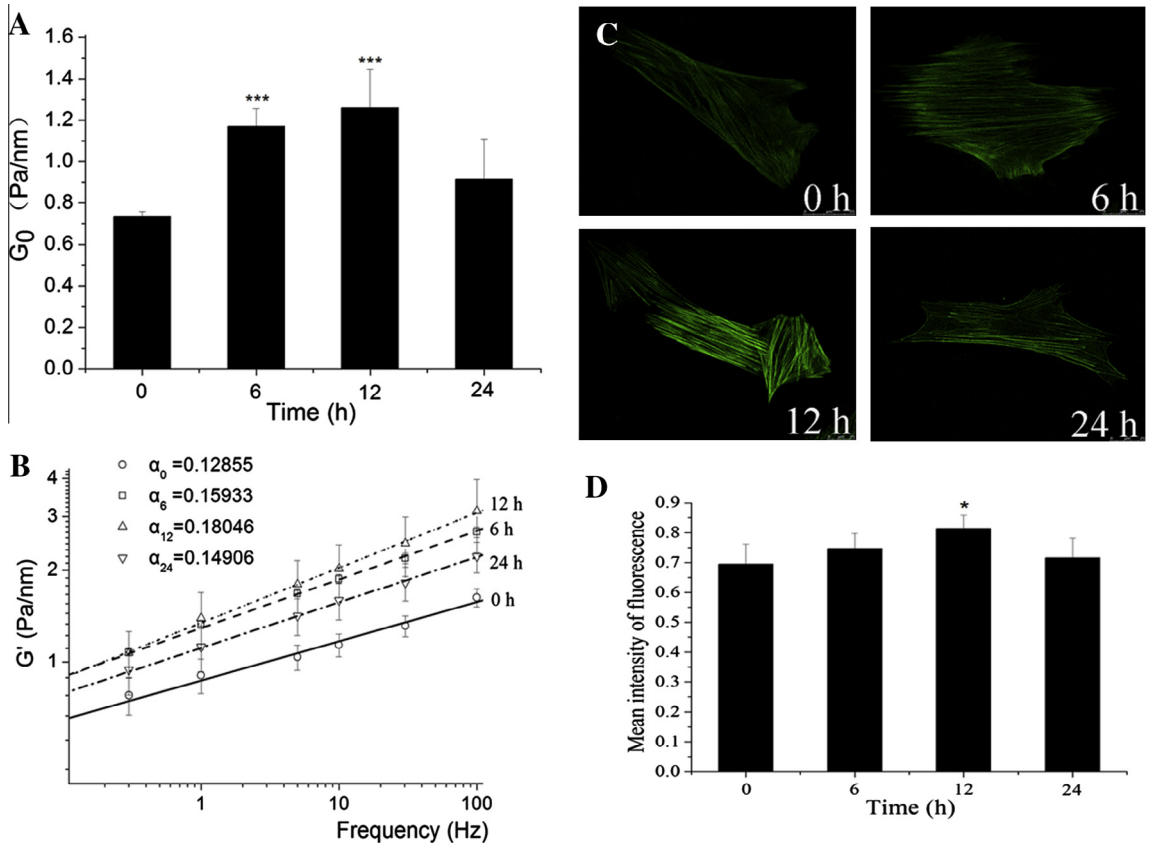

Fig. 3. Cell stiffness and cytoskeletal structure of rMSCs in response to 50 ng/mL MGF. (A) Baseline stiffness (G_0) of rMSCs treated either with or without MGF measured by OMTC at constant 0.3 Hz (from left to right shows 0 (control), 6, 12 and 24 h, respectively). (B) Stiffness of rMSCs measured over the spectrum of frequency (0.1–100 Hz). Data were labeled for rMSCs treated by 50 ng/mL MGF for either (0 h, ○), or 6 h (□), 12 h (△) and 24 h (▽). Power-law function was fitted to the results shown as the straight lines with corresponding slopes (α). (C) Representative images of cytoskeleton protein F-actin in rMSC labeled by FITC-Phalloidin, and visualized by confocal microscopy (×63, oil). (D) The mean optical density of F-actin expression quantified averaged over the area of rMSC in response to MGF. The data bars from left to right represent the quantified mean expression of F-actin in rMSC treated with or without MGF (50 ng/mL) for 0 (control), 6, 12 and 24 h, respectively. The result shows that MGF significantly increased the expression of F-actin compared to control (0 h). ($^{*}p < 0.05$, $^{***}p < 0.001$, $n = 6$).

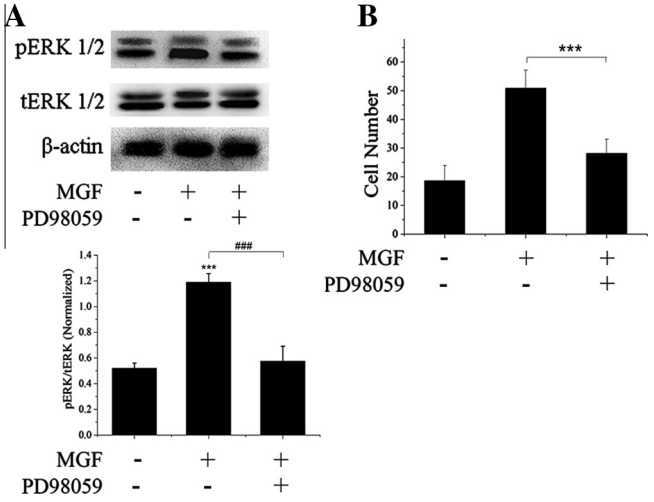

Fig. 4. MGF increased the migration of rMSCs via activating ERK 1/2 signaling pathway. (A) Activation of ERK 1/2 phosphorylation in rMSCs in response to MGF. Upper panel: representative western blot image of phosphorylation ERK 1/2 (pERK 1/2) and total ERK 1/2 (tERK 1/2) expression in rMSCs, together with β-actin as reference marker. Lower panel: the ratio of pERK 1/2 to tERK 1/2 quantified as phosphorylated ERK 1/2. (B) ERK 1/2 is required for MGF-induced rMSCs migration. ($^{***}p < 0.001$, $^{\#\#\#}p < 0.001$, respectively, $n = 5$).

Previously, extracellular-signal-regulated kinase (ERK) could be activated in response to many molecular signals, including G-protein-coupled receptors, src and fyn, has been demonstrated [8]. Subsequently, ERK 1/2 phosphorylated by MGF in various cell types, such as osteoblasts and vascular endothelial [22,23], and ERK 1/2 pathway involved in ACh and SDF-1α-induced MSCs migration were illuminated [11,24]. So it is natural to think MGF-induced rMSCs migration is coupled with ERK pathway. In the present study, MGF activated ERK pathway by increasing ERK 1/2 phosphorylation, and MEK 1/2 inhibitor blocked MGF-induced rMSCs migration by diminishing the ERK 1/2 phosphorylation level stimulated by MGF to that of control was demonstrated, which was similar with previous studies [11,24], suggesting that MGF-induced rMSCs migration is mediated by the ERK 1/2 signaling pathway. These uncover an underlying biological mechanism of MGF-induced rMSCs migration.

In conclusion, our findings suggest in vitro evidence that rMSCs' mechanics and the ERK signaling pathway were involved in MGF-induced rMSCs migration. Our data demonstrated that the phosphorylation level of ERK 1/2, cell traction force, cell stiffness and cell fluidization were increased in MGF-induced rMSCs' migration compared with the control. These together suggest that MGF plays a key role in mediating the migration of rMSCs, possibly by activing the ERK 1/2 signaling pathway, and then further remodeling the cytoskeletal structure to regulate rMSCs mechanics, which may uncover the potential biomechanical and biological mechanisms

of the effect of MGF contributing MSCs migration, and thus may help find MGF-based novel clinical therapeutics to apply MSCs in tissue engineering and regenerative medicine.

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