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Review Article (Invited)

Shape of scaffold controlling the direction of cell migration

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Cell migration plays an important role in the development and maintenance of multicellular organisms. Factors that induce cell migration and mechanisms controlling their expression are important for determining the mechanisms of factor-induced cell migration. Despite progress in the study of factor-induced cytotaxis, including chemotaxis and haptotaxis, precise control of the direction of cell migration over a wide area has not yet been achieved. Success in this area would update the cell migration assays, superior cell separation technologies, and artificial organs with high biocompatibility. The present study therefore sought to control the direction of cell migration over a wide area by adjusting the three-dimensional shape of the cell scaffold. The direction of cell migration was influenced by the shape of the cell scaffold, thereby optimizing cell adhesion and protrusion. Anisotropic arrangement of these three-dimensional shapes into a periodic structure induced unidirectional cell migration. Three factors were required for unidirectional cell migration: 1) the sizes of the anisotropic periodic structures had to be equal to or lower than the size of the spreading cells, 2) cell migration was restricted to a runway approximately the width of the cell, and 3) cells had to be prone to extension of long protrusions in one direction. Because the first two factors had been identified previously in studies of cell migration in one direction using two-dimensional shaped patterns, these three factors are likely important for the mechanism by which cell scaffold shapes regulate cell migration.

Key words: micropattern, cytotaxis, cell protrusion, three-dimensional pattern shape, cell culture scaffold

◀ Significance ▶

Rendering cells prone to extension of long protrusions in one direction and restricting cell migration to a runway can regulate the direction of cell migration.

Introduction

The direction of cell migration is determined by the direction of stimulation, which is dependent on the concentration gradients of migration-inducing substances such as nutrients, cytokines, and extracellular substrates. Cells extend protrusions in the direction of higher concentrations of cell-inducing substances and migrate in that direction. Assays (e.g., chemotaxis assays and haptotaxis assays) can measure cell migration in a single direction in response to these inducers, but these assays are limited to local, short-range migrations [1-3], at least in part because the range of concentrations of migration-inducing factors that can be sensed by cells is relatively narrow. Thus, it is difficult to control the direction of cell migration over greater distances using conventional methods.

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Previous studies on concavo-convex shaped cell scaffolding suggest that these scaffolds may allow cells to migrate in a single direction. Use of these scaffolds may lead to development of new cell migration assays, cell separation technologies, and artificial organs.

The present study focuses on cell scaffolds called micropatterns, especially those with regular concavo-convex micrometer-sized structures fabricated on silicon wafers. Micropatterns with desired shapes on silicon wafers are easily created by photolithography [4-8] and a wide variety of micropatterns have been used to investigate cell morphology [6-8], migration [5-7], and proliferation [7]. All of these properties are dependent on the shape of the micropattern. Cells cultured on a micropattern initially adhere to, protrude from, and migrate along the three-dimensionally sharp edge of the micropattern [6,7] (Fig. 1). This edge, defined as having an angle ≤90º, forms the boundary between the plane constituting the concavo-convex micropattern and the plane that protrudes sharply. Subsequently, these cells extend adhesively in a continuous direction along the flat surface of the micropattern and migrate in that direction [6] (Fig. 1). Earlier cell culture studies of cell morphology [9-31] and migration [20,22,28,29,32] were performed using regular concavo-convex structured micropatterns fabricated on non-silicon wafers, and the results of these studies are still relevant today.

Based on these findings, micropatterns of various shapes were designed and tested for their ability to participate in cell migration in a single direction. This review article is an extended version of the Japanese article [33].

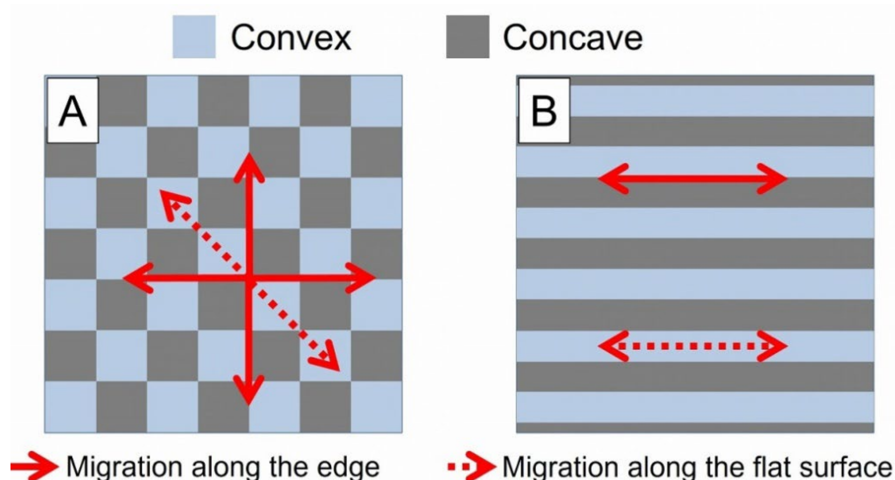

Figure 1 Direction of cell migration on the micropattern. (A) Cell migration on a chequered pattern. (B) Cell migration on a striped pattern. The bright part of each micropattern was convex, whereas the dark part was concave. The boundary between irregularities was a vertical cliff (edge). The direction of each solid red arrow indicates the direction of cell migration along the edge, whereas the direction of each red dotted arrow indicates the direction of cell migration along a flat surface.

Experiment and Results

Strategies for Inducing Unidirectional Cell Migration

To determine the type of micropattern that could result in cell migration in a single direction based only on the shape of the micropattern, this study focused on the strong three-dimensional adhesion of cells to sharp edges [13,14,25,31], and the protrusion and extension of these cells along these edges [6,7]. Because cells migrate in the direction of protrusion extensions [34,35], successful arrangement of these sharp edges, and controlling the direction of extension of these protrusions, may induce cells to migrate in only one direction. This ability may also be enhanced by making this sharp edge an anisotropic periodic structure, with a cycle approximately the same size as a cell being most effective. Micropatterns with these sharp edges were designed and fabricated, resulting in the migration and uneven distribution of NIH 3T3 cells cultured on these micropatterns. The finding, that uniformly seeded cells were unevenly distributed after culturing, was indicative of cell migration in only one direction.

Induction of Unidirectional Cell Migration

Extensive experiments were performed to determine a micropattern that results in unidirectional cell migration. Although isosceles triangles were regarded as the basic form of anisotropic periodic structures, a pattern in which these structures were simply arranged closely had absolutely no effect (Fig. 2A). Elements of a striped pattern were therefore included in the isosceles triangle pattern, thereby limiting cell migration to one dimension parallel to the stripe structure

(e.g., Fig. 1B). Evaluation showed that cell migration was limited to one dimension (Fig. 2B). Detailed time-lapse evaluation of cell migration patterns cells showed that these cells were located both inside and outside the groove. Additionally, slight anisotropic migration was seen in the groove. Outside the groove, however, these cells migrated at a high speed in both directions on which flat surfaces were continuous (i.e., the direction of overlap of isosceles triangles). These findings indicated that cell migration in a single direction required a reduction in the number of cells outside the groove.

Cells could transfer from outside to inside the groove by migrating along the edges (Fig. 1A, B). Specifically, the ratio of the length of the base to the length of the equilateral sides of an isosceles triangle was increased, and the direction of cell migration outside the groove was made perpendicular to the continuous direction of the groove. These steps were thought to prevent cell migration in both directions, with cells outside the groove being directed to inside the groove. None of the cells migrated at high speed in both directions outside the groove, with most cells migrating inside the groove (Fig. 2C). However, cells became trapped in the narrow part of the groove, causing migration to stop there. The narrow part of the groove was located between the base angles of the isosceles triangles adjacent to each other between the grooves.

Shifting the positions of the base angles of the adjoining isosceles triangles that caused the groove to narrow overcame this drawback. Following completion of this micropattern (Fig. 2D) [36], the cells in the groove were no longer trapped and began to migrate to the right. Maintenance of this basic shape resulted in cell migration in a single direction, even if cell size or spacing was slightly different. The micropatterns that exhibited optimum cell migration in one direction consisted of equilateral triangles, with each side measuring 18.3–23.9 μm, a base measuring 19.7–44.9 μm, between-triangle intervals overlapping by 10% of the height measuring 7.2–15.7 μm, angles between each equilateral side and the base measuring 19.0–60.8°, tangential lines between adjacent triangle rows measuring 3.2–9.3 μm, a ratio of the base to each equilateral side of the isosceles triangle ≥1, and triangular prisms approximately 21 μm in height. Despite changes in shape parameters, cell migration in one direction was maintained as long as the basic shape shown in Figure 2D was maintained. These findings also confirmed that an anisotropic structure with a period equal to or smaller than the spreading cell size was effective for unidirectional cell migration. This was highly unusual, inasmuch as previous studies have evaluated cell migration in one direction using two-dimensional patterns [37-41], with none focusing on cell migration in one direction by cell-adhesive three-dimensional shapes. Although studies used the term “3D microchannels”, the adhesion area was in two dimensions, making it a study using a two-dimensional pattern [38,39]. In another study, the cells migrated in a two-dimensional plane, and a three-dimensional cell-adhesive scaffold was not utilized [42]. Therefore, we applied for a patent for this shape on 6th November 2013, with this shape later patented in Japan (Patent No. 6128620) and the U.S. (Patent No. 9,958,429 B8).

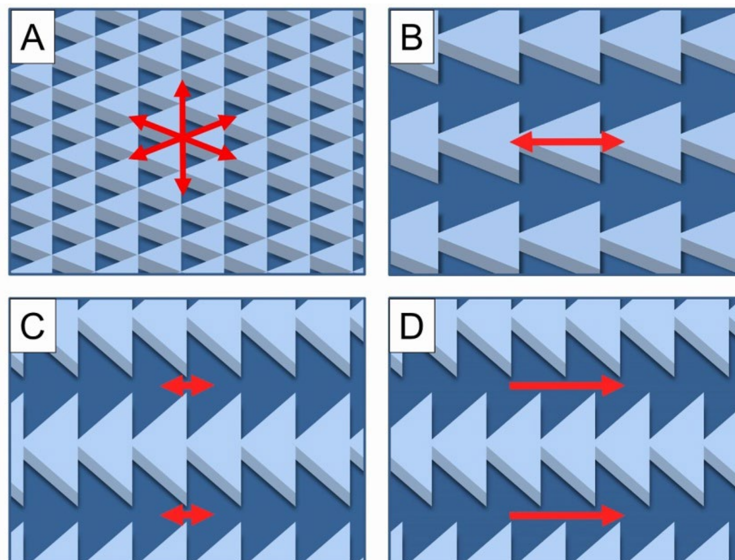

Figure 2 Process of optimizing the micropattern shape. (A) Cell migration on a pattern of closely arranged isosceles triangles. (B) Cell migration on a pattern of isosceles triangles arranged in stripes. (C) Cell migration on isosceles triangles with a higher ratio of the base to the equilateral side. (D) Cell migration on isosceles triangles in which the position of the base of adjacent isosceles triangles was shifted between grooves (completed). The bright part of each micropattern was convex, and the dark part was concave. The direction of the red arrow indicates the direction of cell migration.

Confirmation of Unidirectional Cell Migration by Uneven Distribution of Cells

Another important aspect of this study was to confirm unidirectional cell migration. In total, 507 types of micropattern were prototyped, and cell migration was evaluated for all of these. To efficiently evaluate a large number of micropatterns, the cells were uniformly seeded in 1 mm^2 micropattern regions on a 1 cm^2 silicon wafer that had been hydrophilically treated. The uneven distribution of these cells after culture for 72 h was considered indicative of cell migration in a single direction. Figure 3 shows an example of the uneven distribution of NIH 3T3 cells cultured on the final completed micropattern. When we compared the cell densities in the right and left areas in Fig. 3, we found that the cell densities in the right areas were significantly higher than those in the left areas (Fig. 4). Based on this, it was possible to ascertain how cells are unevenly distributed to the right, confirming cell migration in a single direction [36].

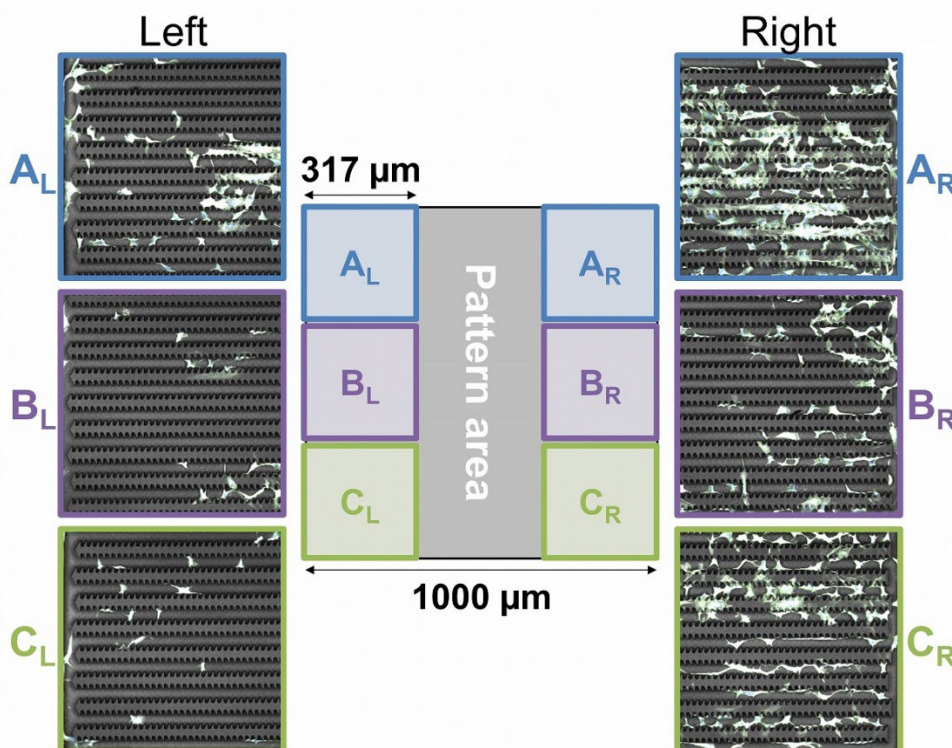

Figure 3 Confirmation of uneven distribution of cells in isolated pattern regions. NIH 3T3 cells (green: phalloidin-stained actin filaments, blue: DAPI-stained nuclei) uniformly seeded in a 1 mm^2 pattern region on a 1 cm^2 silicon wafer and cultured for 72 h were evaluated by laser scanning confocal microscopy. The observation locations were on the left (A_L, B_L, C_L) and right (A_R, B_R, C_R) areas of each micropattern.

Discussion

The association between micropattern shape and cell migration in a single direction, resulting in uneven cell distribution, was evaluated using time-lapse videos, which showed that 94% of cells were in the groove, and that migration toward the right (i.e., the direction from the apex angle to the base of an isosceles triangle) was high [36]. Cells in these grooves acquired characteristic adhesion morphologies that were not present on flat surfaces (Fig. 5). Cells clinging to the edges of multiple projections lined up like saw blades in a groove, and acquired a unique adhesion morphology, with extensions of long protrusions [36]. The unique morphologies of cells in the grooves may depend on the scaffold used, which have three types of sharp edges (Fig. 6 (1) – (3)). Detailed evaluation of cell migration and adhesion morphology showed that a few cells outside the groove (above the pattern) extended protrusions in the direction of the red arrow along the two equilateral sides (Fig. 6 (1)) and the base (Fig. 6 (2)), with adhesive extensions in a direction orthogonal to the groove. Additionally, cross-sectional evaluation showed the cells in the groove remained at a middle depth (Fig. 5), with very few cells reaching the bottom. If the protrusion extension in Figure 6 (3) was in the same direction (downward) as that in Figure 6 (1) and (2), many cells must have reached the bottom of the groove; however, this did not occur, suggesting that the extension was in the opposite direction (upward).

These results suggest that protrusions of NIH 3T3 cells extended along the edges of Figure 6 (1) – (3), and adhesively extended in the direction of the arrow in this figure. Thus, these cells may have moved into micropatterned grooves, resulting in a unique morphology allowing them to cling to the tips of multiple projections. Although difficult to see in Figure 5, cells clung to all sharp edges ((1) – (3)) via countless fine protrusions. These cells were thought to adhere firmly to further edges, and extend thick and long protrusions to the edges of the adjoining and projecting parts on the right-hand side of the groove. Migration to the right may have resulted from the sum of the geometric vectors for the extension of the protrusion in Figure 6 (1) – (3) being greater in the right-hand direction. In addition, the depth of the groove (i.e., the height of the triangular prisms), the width of the groove separating the adjacent edges, and the vertex where the three sharp edges ((1) – (3)) meet may also play extremely important roles in determining the direction of protrusion extension. Future studies should use time-lapse observation at high magnification to investigate the direction and frequency of protrusion extension along the three edges, and the role of the vertex at which the edges intersect.

The three-dimensional shape identified in the present study that causes cells to migrate in one direction was similar in part to previously described non-adhesive tilted micropillars [42]. The anisotropic three-dimensional structures in the micropattern in the present study and in previously described micropillars have a periodic structure with a size equal to or less than that of a cell, but in contrast to the micropatterns, cells do not adhere to the micropillars. In addition, research on cell migration in one direction was assessed with two-dimensional shapes prior to assessment using three-dimensional shapes. Although several high-impact papers on using two-dimensional shapes were withdrawn [43-45], others were not [37-41], with each of these shapes also differing in the shape, size, arrangement, and spacing of cell adhesion regions. The two- [37-41] and three-dimensional [36] scaffolds were similar in that migration of cells was limited to a runway as wide as a cell, and that having anisotropic periodic structures equal to or less than the spreading cell size were effective for unidirectional cell migration. Future studies should include further development of anisotropic cell migration technology by incorporating effective elements of two-dimensional scaffolding into three-dimensional scaffolding.

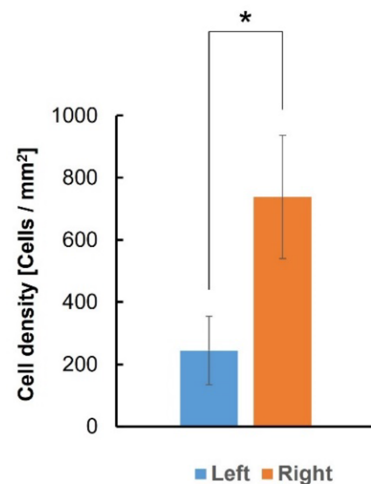

Figure 4 Cell densities in the left (A_L, B_L, C_L) and right (A_R, B_R, C_R) areas in Fig. 3. The cell densities are presented as the mean ± standard deviation. An unpaired t test was used to compare cell densities. The total cell number used for calculation of the averaged cell densities was 297. P values of < 0.05 were considered significant (n.s., not significant; *, $p < 0.05$; **, $p < 0.01$; and ***, $p < 0.001$).

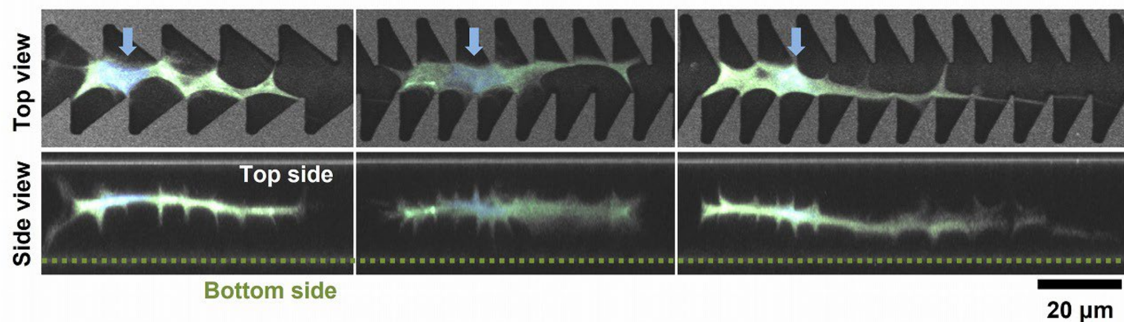

Figure 5 Characteristic morphology of cells in the grooves. Superimposed fluorescence images of NIH 3T3 cells (green: Phalloidin-stained actin filaments; blue: DAPI-stained nuclei) and a reflection image of each micropattern on confocal laser scanning microscopy. The top views show the micropatterns and the cells observed directly above, and side views show the micropatterns and cells seen from the side. Blue arrows indicate the locations of the nuclei.

Conclusion

The present study showed that the three-dimensional shape of a micropattern was responsible for cell migration in a single direction, such that cells were distributed unevenly. Cells are thought to extend protrusions along the sharp edges

of such micropatterns in a single direction, migrating for as long as the micropattern continues in that direction. The shape of the scaffold developed in this study is highly durable because it can be integrated with the base material of every scaffold, with the advantage of reduced manufacturing costs if a mould is used. This micropattern can be applied to various substrates and devices, including cell separation technology and artificial organs.

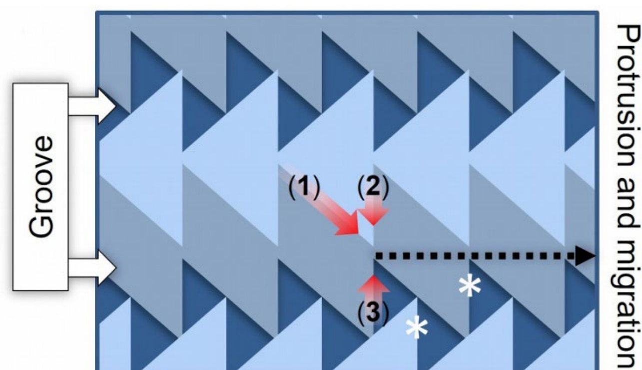

Figure 6 Diagram showing three types of sharp edges, and the direction of extending protrusions. (1) Edge on an equilateral side. (2) Edge on the base. (3) Side edge of a triangular prism. The direction of the red arrow is the predicted direction of the extending protrusions on each edge. The asterisk represents the edges of the adjoining and projecting parts on the right-hand side. The dotted line shows the direction of extending protrusions and cell migration.

Conflict of Interest

The authors have no conflicts of interest directly relevant to the content of this article.

Author Contributions

H. Sunami, Y. Sunami, and H. Kishimoto directed the entire project and co-wrote the manuscript.

Data Availability

The evidence data generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

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