New and Notable

Dimensional Control of Cancer Cell Migration

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Cell migration is a fundamental cellular function that underlies numerous diverse biological processes, including tissue patterning, morphogenesis, immune response, and cancer metastasis. While earlier studies emphasized the importance of chemical factors in cell migration, accumulating evidence suggests that the physical cues of the microenvironment also influence cell motility, including the local stiffness and microstructure of the extracellular matrix (ECM). Much of what we know about the physical and molecular mechanisms of cell locomotion stems from in vitro studies using two-dimensional, ECM-coated surfaces (1). However, a wide range of cells, such as fibroblasts in connective tissues and locally invading cancer cells in the stromal matrix near a tumor, migrate in three-dimensional and even one-dimensional environments. Accumulating evidence suggests that the dimensionality of the migratory environment affects cell motility mechanisms (2). For instance, features important in two-dimensional locomotion, such as stress fibers and focal adhesions, are significantly reduced in motile cells in a three-dimensional matrix, whereas others critical to three-dimensional migration, such as nuclear deformation and matrix metalloproteinase production, have little or no role in two-dimensional cell motility (3–8).

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Cell-derived and reconstituted ECM gels have been used to study three-dimensional cell migration. Microfabrication techniques have been employed to study cell migration on one-dimensional lines (3). Although true one-dimensional lines rarely occur in vivo, one-dimensional and three-dimensional assays share certain similarities such as similar cell morphology, and reduced numbers of stress fibers and focal adhesions relative to two-dimensional surfaces. Cells typically migrate in vivo through three-dimensional collagen matrices and three-dimensional channels. Three-dimensional longitudinal tracks with bordering two-dimensional interfaces (i.e., channels) are formed by large anatomic structures covered by a basement membrane, including myofibers, fat tissue, perineural, and perivascular spaces (9). Similarly, three-dimensional tracks are formed by bundled collagen fibers in fibrillar interstitial tissues (3,9). Importantly, tumor cells have been reported to migrate through such three-dimensional tracks in vivo.

Balzer et al. (10) recently fabricated a microfluidic-based migration device to examine chemotactically driven cell migration through channels of different widths. Migration through wide channels (i.e., W larger than cell diameter, d_{cell}) recapitulates the hallmarks of two-dimensional locomotion, whereas migration through narrow channels (i.e., $W \ll d_{cell}$) mimics cell motility through physically constricted spaces encountered in vivo (9). This study showed that, in line with observations made using one-dimensional lines or three-dimensional assays, dorsoventral polarity, stress fibers, and focal adhesions are markedly attenuated by confinement (10). Consistent with data obtained using one-dimensional lines, inhibitors of myosin or Rho/ROCK did not impair migration through 3-μm channels (confinement), even though these treatments repress motility on two-dimensional surfaces. Remarkably, the migration of metastatic breast cancer cells through narrow channels persists even when F-actin is disrupted or myosin II is inhibited, and depends largely on microtubule dynamics (10). Microtubule assembly may provide a driving force for confined and one-dimensional migration. Despite these similarities, one-dimensional, three-dimensional, and confined migration should not be considered alike.

In this issue of the *Biophysical Journal*, Chang et al. (11) demonstrate a novel myosin-dependent mechanism of "dimensional-sensing" by mouse fibroblasts. A migrating cell traveling on two-dimensional rectangular surfaces alternating with narrow one-dimensional patterned surfaces will spend significantly more time on the two-dimensional surfaces. Consistent with earlier results, cells on one-dimensional surfaces display fewer and smaller focal adhesions as well as organized stress fibers, and in turn generate much lower traction forces on the underlying surface than cells on narrow patterns. The relative effect of myosin II inhibition is much smaller in one dimension than in two. Constriction of cells from a two-dimensional to a one-dimensional surface depends critically on myosin II-based contractility (11). Importantly, dimensional sensing is mostly lost in *ras*-transformed cells, where *ras* is an oncogene. This defect may contribute to the invasive phenotype of transformed cells in cancer metastasis. This defect may be due, in part, to a loss of regulatory control of *ras* (11). *Ras* transformation may reduce cellular dimensional sensing by decreasing myosin II expression.

These studies may mimic cancer cells peeling off from the surface of a primary tumor, which is essentially two-dimensional at the length scales of a cell, and move along collagen fibers as suggested by intravital

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microscopy in a live mouse, i.e., a 2D-to-1D switch of dimensions (11). Because different organs and tissues may present different local dimensions at the scale of a cell (9), it would be interesting to study other physiopathologically relevant changes in dimensions, i.e., 2D-to-3D and 1D-to-3D, and determine whether the same mechanism of myosin-dependent dimensional sensing elucidated by Chang et al. is at play and whether *ras* transformation abrogates the ability of migrating cells to sense these dimensional changes.

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