Microtrack migration: insights into 3D cell motility. Focus on “Comparative mechanisms of cancer cell migration through 3D matrix and physiological microtracks”

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THE METASTATIC SPREAD OF CELLS from solid tumors to distant sites, leading to the consequent development of secondary lesions, has been estimated to be the primary contributory factor in as many as 90% of cancer patient deaths. As a result, there has been considerable interest in understanding the processes that promote cancer cell dissemination to improve diagnosis and evaluate risk, as well as to identify potential drug targets that could be inhibited with therapeutic agents to reduce cancer spread (3). The ability of tumor cells, either as single cells or in collective groups, to break away from the primary mass and invade surrounding tissue is a critical element of cancer metastasis leading to lethal disease. There has been a great deal of research focused on cancer cell migration in two-dimensional (2D) and three-dimensional (3D) experimental contexts that has revealed the complex coordination between biophysical and biochemical features of migratory cells and the extracellular matrix (ECM) (6). In particular, the role played by proteases, such as matrix metalloproteases (MMP), in ECM remodeling to enable tumor cell migration has been well characterized. However, one relatively unstudied aspect is how cells migrate through ECM microtracks.

It has been shown that channel-like gaps in the ECM, which may be naturally occurring or result from proteolytic stromal matrix degradation, provide paths for MMP-independent cell migration (2, 8). “Leading” path-generating cells that create microtracks that enable “follower” cells to migrate may be stromal, such as cancer-associated fibroblasts (4), or may be tumor cells that have the required proteolytic activities (7). To characterize how cancer cells migrate through ECM microtracks, Kraninger-Rush et al. (5) developed an in vitro system using microfabricated collagen I tracks to model ECM microtracks observed in vivo. Tumor cells that were unable to migrate through 3D collagen matrix moved rapidly through fabricated cell-sized microtracks. In addition, invasive cancer cells that had been able to move through 3D collagen had higher migration speeds when moving within microtracks (5). These observations indicated that microtracks facilitate migration through the ECM, consistent with their having an important role in promoting metastasis.

In this issue of American Journal of Physiology-Cell Physiology, Carey et al. (1) extend their previous findings by validating the resemblance of fabricated collagen I microtracks to the channel-like gaps observed in mammary stroma ECM in vivo. By implanting MDA-MB-231 human breast cancer cells into murine mammary fat pads, they found that cells invading the adjacent stroma produced empty channel-like gaps roughly as wide as individual cells, which enabled follower cells to migrate through the ECM, paralleling the ability of cells to move through cell-width microfabricated collagen I tracks. In vitro, increasing 3D collagen density significantly decreased cell speed and motile fraction, while invasion via microtracks was not affected by the density of the surrounding matrix, because microtracks provided paths of least resistance that did not require additional ECM remodeling, traction force generation, or physical deformation of cells or nuclei.

Moreover, Carey et al. (1) examined the mechanisms employed during cancer cell migration through 3D ECM or via microtracks (Fig. 1). Using a β1-integrin-blocking antibody to characterize the role of cell-matrix adhesion in microtrack migration, they found that single-cell microtrack migration speed was unaffected by β1-integrin inhibition but that cell morphology changed from predominantly elongated to a pattern of oscillation between elongated and rounded forms. This observation indicates that although migration was independent of cell shape, persistence of the mesenchymal-type elongated shape adopted by cells within microtracks requires β1-integrin activity, possibly for Rac1 activation to promote membrane protrusions that drive cell elongation (6). The morphological oscillations between elongated and rounded (a morphology shown previously to be induced by Rho-mediated actin-myosin contraction) suggest that activation of Rac or Rho is intrinsically wired to act as a bistable switch that generates morphological plasticity responsive to extracellular conditions. Thus, when β1-integrin was permitted to engage with the ECM, the switch was positioned to the Rac activation state to establish the elongated cell shape. The possibility remains that other cell surface proteins that associate with the ECM (e.g., integrin or nonintegrin receptors) may substitute for antibody-inhibited β1-integrin to enable shape-independent microtrack migration. In contrast to the lack of effect in cells migrating through microtracks, β1-integrin inhibition decreased cell elongation and migration speed in 3D collagen, indicating a requirement for β1-integrin-mediated cell-matrix adhesion for migration through the ECM.

In studying the influence of actomyosin contractility in migration through microtracks, Carey et al. (1) found that pharmacological inhibition of Rho, Rho-associated protein kinase, or myosin light chain kinase reduced traction force but had no effect on the motile fraction or cell speed, indicating that traction forces are not required for microtrack migration. However, when myosin ATPase activity was inhibited directly, microtrack migration speed was significantly reduced, suggesting that a minimal level of myosin-mediated contractility is required for microtrack migration, likely by facilitating retraction of the lagging end. In contrast to microtrack migration, application of all contractility inhibitors significantly reduced the motile fraction in 3D matrix migration, possibly resulting
from a need for force generation to drive ECM remodeling and for traction-mediated movement.

Further analysis with pharmacological inhibitors revealed that both microtrack and 3D matrix migration were dependent on actin and microtubule cytoskeletal dynamics. Cell movement, in terms of migration speed and motile fraction, through each type of environment was found to be driven by actin polymerization at the leading edge to drive protrusions, with microtubules supporting protrusion and elongation.

The processes that contribute to the metastatic spread of cancer cells have been intensively studied; yet the most information has been gleaned from experiments that did not differentiate between leader and follower cells. By comparing migration through 3D matrix with movement through microtracks, Carey et al. (1) have revealed the adhesion and actin-myosin contraction requirements for cell migration along preexisting or cell-derived paths and have identified cell interactions with the ECM via β1-integrin as an important modifier of invasive cell morphology, which enables tumor cells to use different migration mechanisms in response to varying microenvironmental contexts. Increased understanding of invasive cell migration, in terms of differences between leader and follower cells and in different external contexts, is necessary to identify new therapeutic targets and to realistically evaluate their clinical potential.

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