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New and Notable

Swimming Cells Can Stay in Shape

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Cell motion is necessary for many physiological phenomena, including reproduction, development, wound healing, and the immune response. Cell motion is also involved in many pathological processes, including cancer and cardiovascular disease. Over the past decades, we have learned that cells have a variety of mechanisms for movement at their disposal. Mounting evidence suggests that the specific mode of migration chosen by cells may depend on a balance between cell adhesion to the substrate, actin-based protrusions at the cell's leading edge, and actomyosin contractile forces and that this balance may be shifted by the microenvironmental conditions or cell type (1). Some of the specific mechanisms that have been observed for mammalian cells include classic mesenchymal migration on two-dimensional surfaces (2), amoeboid migration (3), a nuclear piston-based mechanism (4), an osmotic engine model (5), and a friction-dependent "chimneying" mechanism (6). For example, in low-adhesion environments, some cells adopt the amoeboid migration mode, which is accompanied by rapid cell shape changes over time and is typically faster than mesenchymal migration. On the other hand, bacteria, microalgae, and mammalian gametes "swim" in fluids, completely in the absence of adhesion to a surface, through propulsion by a flagellum (7) or shape deformations (8). In general, the notion that mammalian cells can swim without a flagellum has been, at best, understudied and in many cases widely rejected. Nonetheless, whether mammalian cells can swim and, if so, how they do it have remained open questions in the field of cell migration.

In this issue of *Biophysical Journal*, Aoun et al. provide exciting theoretical and experimental evidence for a new model in which amoeboid swimming by lymphocytes is propelled by molecular paddling (9). This article demonstrates that lymphocytes are motile on Pluronics-coated, nonadhesive solid substrates and that this motility mode is not propelled by cell shape changes over time. Contrast interferometric imaging revealed a bright contact zone between the cells and substrate, which suggests the existence of a thin layer of fluid between the cells and the substrate. Lymphocytes were even able to transfer rapidly between adherent migration and swimming motion when challenged with patterned substrates with alternating adhesive and nonadhesive stripes. The authors were careful to rule out effects of flow within the dish and hydrodynamic coupling with the substrate using a precision-controlled microfluidic channel, cell-density-matched culture media, and microscope tilt, and they also demonstrated that the swimming motion was unique to polarized, motile cells and did not apply to inactive and round cells that were passively diffusing.

One might expect that increasing the cell culture media's viscosity would cause cells to swim more slowly (imagine a competitive swimmer swimming in room temperature water versus olive oil). Intriguingly, Aoun et al. (9) reported that the swimming mechanism was viscosity independent, at least up to 100 times the viscosity of the cell culture media. The explanation for this phenomenon leads us to the part of the cell responsible for the swimming mechanism—the cell cortex, whose viscosity is much higher than the typical cell culture media, and hence, the viscosity of the surrounding environment would have to approach the viscosity of the cell cortex to have an effect. Using a series of drugs to perturb actin and myosin in swimming cells, the authors concluded that the actin-rich lamellipod was largely responsible for propelling the swimming motion, whereas the uropod was significantly less involved. The authors considered a series of theoretical models, in which cell motion was modeled by the following: 1) combining deterministic swimming and (translational and rotational) random noise; 2) applying active forces to an elastic capsule to simulate bleb-like protrusions; 3) considering the driving force for actin cortex flow

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as the pressure gradient along the cell surface, generated by overpressure at the cell front due to actin accumulation and under pressure at the cell rear because of myosin-driven contractions; and 4) considering the transfer of cortex retrograde flow to fluid outside the cell (the molecular paddling mechanism). Intriguingly, the mechanism of swimming described in Aoun et al. (9) was found to be propelled by rearward and inhomogeneous treadmilling of the cell external membrane, leading to "paddling" of transmembrane proteins that are linked to and advected by the cell cortex. Once reaching the cell rear, the paddling integrin molecules are recycled through vesicular transport back to the molecular "sink" at the front of the cell. The cycle of treadmilling and vesicular transport was on the order of the swimming timescale, further supporting this mechanism. Strengths of the work of Aoun et al. (9) include the incorporation of experimentally testable parameters in their theoretical model of molecular paddling; matching of timescales between swimming, molecular treadmilling, and vesicular transport; and coordination between experimental and theoretical data.

Before the work of Aoun et al. (9), only two studies reported swimming of leukocytes in the absence of adhesion (10,11). One of these studies did not explore mechanisms of the nonadherent migration (10), although the second study reported an "artificial swimming mode" that involved optogenic activation of contractility at the cell rear (11). Aoun et al. (9) now contribute to the field a molecular paddling mode of swimming with support from an elegant theoretical model along with extensive experimental evidence in nonengineered lymphocytes.

Although the ability of lymphocytes to swim via a molecular paddling mechanism is intriguing, one may wonder whether this type of motility is physiologically relevant and, if so, in what physiological microenvironments it takes place. Another question is whether any other cell types exhibit this type of swimming motility or whether we could use what Aoun et al. (9) learned about swimming in lymphocytes to engineer other cell types to utilize this mode of swimming. On a mechanistic level, it could be helpful to identify the full set of transmembrane proteins (beyond integrins) contributing to the paddling motion. Indeed, many open questions remain about how swimming cells use molecular paddling, but this study is yet one more that points to the robustness of cells and how they "know" which mode of motility to adopt as a function of their environment.

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