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Redefining confined cell migration through shape–volume dynamics

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Cell migration through physically constrained spaces is central to many physiological and pathological processes, from tissue formation to cancer metastasis [1,2]. To navigate dense extracellular matrices and narrow tissue spaces, cells must continuously deform their shape while maintaining essential physiological functions. Although confinement often enhances migration speed and directional persistence [2–4], the physical principles that enable cells to adapt to such environments remain incompletely understood. In particular, how cells coordinate shape remodeling with volume regulation during migration has emerged as a fundamental question in cellular mechanobiology.

Traditionally, studies of confined migration have largely focused on morphological adaptations. Elongated cell shapes, nuclear deformation, and specialized protrusions have all been identified as hallmarks of migration under physical constraint [4–6]. These observations have greatly improved our understanding of how cells respond to their surroundings. However, morphology alone does not explain why some cells migrate more effectively than others. The key challenge is therefore not merely to identify the structures associated with migration, but to understand the dynamic principles governing cellular adaptation to confinement.

Recently, in an Express Letter published in *Chinese Physics Letters* [7], Xie *et al.* shift attention from static morphology to dynamic regulation and suggest that the temporal coordination between cell shape and volume may represent a previously overlooked descriptor of migratory efficiency. The authors introduced a volume–surface dynamic correlation coefficient, C, defined as the slope relating normalized rates of volume change to surface area change. C measures how closely volume fluctuations accompany surface remodeling. The authors find that physical confinement reduces C. In other words, cells migrate most efficiently not when shape change and volume regulation become more tightly coordinated, but when their coupling becomes weaker. This challenges the expectation that efficient migration requires tighter coordination between cellular deformation and volume regulation. Instead, cells migrate more effectively when they are capable of repeatedly changing shape without requiring proportionally large volume adjustments. From this perspective, the coefficient C represents more than a descriptive parameter. It captures how cells coordinate mechanical deformation with volume homeostasis during migration. To explain the reduced coupling observed under confinement, the authors propose a mechano-osmotic feedback mechanism in which surface remodeling perturbs the mechanical load on the membrane–cortex system, while volume regulation responds through ion and water transport with a finite delay. Under confinement, the apical interface becomes mechanically engaged, accompanied by increased apical membrane tension, vinculin redistribution, and enhanced nuclear accumulation of YAP. By sharing the mechanical load associated with surface remodeling, the apical boundary reduces local membrane-tension buildup and diminishes the need for immediate osmotic compensation during deformation. Consequently, cells can undergo continuous shape changes while maintaining relative volume stability, resulting in a lower C. Together, these findings suggest that efficient confined migration relies on a mechano-osmotic adaptation mechanism that reduces the energetic costs of shape remodeling.

The robustness of C as an integrative biophysical descriptor was further tested through a set of physical and chemical perturbations. The authors independently targeted matrix metalloproteinase activity, actomyosin contractility, Na^+/K^+-ATPase function, and volume-regulated anion channels. Although these interventions affect distinct pathways, they produced a consistent outcome: migration decreased while C increased. This convergence suggests that weak volume–surface coupling is not a byproduct of a specific pathway but a common characteristic associated with efficient migration in confined space.

Beyond its specific findings, this work expands the conceptual view of cell migration. Cell migration is often described as a problem of force generation and force transmission [8,9]. The authors highlight a complementary principle: migration may also depend on how flexibly cells coordinate distinct regulatory systems operating on different timescales. In this view, volume regulation is not a homeostatic process that passively follows deformation but an active participant in migratory adaptation, directly affecting the cellular response to confinement and mechanical stress. This interpretation is consistent with accumulating evidence that volume regulation contributes to invasive behavior, immune-cell trafficking, and migration in complex three-dimensional environments [10]. In these settings, cells must balance competing mechanical and physiological constraints. Whether weak volume–surface coupling can serve as a general mechanism for resolving such competing demands remains an open and intriguing question.

Looking forward, several important questions emerge from this work. A crucial next step is to determine whether weak volume–surface coupling is a universal physical strategy for complex migration. Validating this framework requires moving beyond simplified confinement assays into fully embedded 3D matrices and *in vivo* microenvironments. These complex environments will clarify how matrix mechanics, geometry, and tissue architecture regulate the coefficient C, and whether it governs broader scaling relationships across cell types. Another important challenge is to identify the molecular and biophysical mechanisms that regulate C. Integrating membrane mechanics, adhesion-mediated force transmission, osmotic regulation, ion and water transport, and cytoskeletal remodeling into quantitative mechano-osmotic models may ultimately allow C to be predicted from first principles [11]. Finally, it remains unclear whether reduced

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volume–surface coupling merely accompanies efficient migration or actively contributes to invasive behavior. Addressing these questions may ultimately determine whether C can serve as a physically interpretable indicator of migratory adaptability and metastatic potential.

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