Generation of compartmentalized pressure by a nuclear piston drives 3D cell motility

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Abstract

Cells use actomyosin contractility to enlarge and strengthen adhesions, as well as move their cell body through three-dimensional (3D) extracellular matrix. Contractility also governs the type of protrusion that cells use to migrate in 3D, but the mechanisms by which it regulates protrusion formation and the mode of migration are unclear. To test the hypothesis that actomyosin contractility controls intracellular pressure to dictate the mode of 3D migration, we directly measured the hydraulic pressure exerted by the cytoplasm in primary fibroblasts migrating using either lamellipodial or lobopodial protrusions. Pressure was significantly elevated and compartmentalized in lobopodia (to ~2750 Pa), with the nucleus separating this anterior high pressure compartment from a low-pressure zone (~800 Pa) at the posterior of the cell. In contrast, low pressures were found both forward and back of the nucleus in fibroblasts using lamellipodia to migrate in 2D and 3D environments (~400 and 700 Pa, respectively). The compartmentalized elevated pressure in lobopodial cells corresponded with a polarized distribution of vimentin filaments and myosin IIA and IIB in front of the nucleus and the ability of the nucleus to accelerate periodically away from the trailing edge. Severing the nucleus from intermediate filaments by knocking-down the nucleoskeleton-cytoskeleton linker protein nesprin 3 reduced and equalized the intracellular pressure, switched cells to lamellipodia-based migration, and abolished the independent movement of the nucleus. Inhibiting contractility dissociated vimentin filaments from the nucleus and reduced the hydraulic pressure, switching cells from lobopodial to lamellipodial motility. In contrast, fibroblasts on rigid 2D surfaces used contractility to increase the size of their focal adhesions without increasing their hydraulic pressure. These data indicate that primary fibroblasts migrating in 3D extracellular matrix can activate actomyosin contractility to couple intermediate filaments to nesprin 3 and tow the nucleus forward,
thereby increasing hydraulic pressure between the nucleus and the leading edge. Additionally, the mechanism by which contractility controls hydraulic pressure appears to be distinct from how it generates traction force.

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