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CELL MIGRATION

Nuclear envelope ruptures as cells squeeze through tight spaces

> migration of cells through confining spaces involves the rupture and ESCRT III-dependent resealing of the nuclear envelope

Some migrating cell types, and particularly metastatic cancer cells or immune cells, may require passing through narrow intercellular spaces to penetrate tissues. The large nucleus of migrating cells is relatively rigid, and thus its deformation may constitute a limiting step during migration through a densely packed microenvironment. The nuclear envelope disassembles transiently during mitosis, but it is otherwise thought to remain intact during interphase. Now, in *Science*, two independent studies report that the nuclear envelope undergoes rupture followed by rapid ESCRT (endosomal sorting complexes required for transport) III-dependent resealing during immune and cancer cell migration.

To study the mechanisms allowing cells to migrate through confined spaces, Denais *et al.* and Raab *et al.* designed *in vitro* migration assays consisting of microchannels with constrictions of varying widths, mimicking the interstitial gaps observed *in vivo*. When using human dendritic cells and/or different types of cultured human cancer cell lines expressing green and/or red fluorescent proteins fused to a nuclear localization signal (NLS), they observed that the GFP or RFP signal was rapidly released into the cytoplasm when nuclei were passing through a narrow constriction (~3 μm), indicating the loss of nuclear envelope integrity as a result of its rupture upon passage through narrow gaps.

Clive Chilvers / Alamy

Both groups also observed a marked decrease in nuclear GFP signal during cellular migration *in vivo*: in fibrosarcoma cells invading collagen-rich mouse dermis, and in dendritic cells migrating in a mouse ear explant.

When analysing in further detail the timing and location of nuclear envelope rupture, both groups found that it occurred predominantly at the leading edge of nuclei, and that it was preceded by, or coincided with, the formation of nuclear membrane protrusions (blebs). Moreover, they observed that nuclear pores were excluded from the blebs, and that the nuclear lamina had defects where the blebs formed.

Importantly, nuclear envelope rupture was transient, as shown by the redistribution of the NLS–GFP signal, indicating that cells can restore nuclear membrane integrity during interphase. Both groups found that resealing of nuclear envelope openings involves the ESCRT III machinery, previously reported to mediate the resealing of nuclear envelopes at the end of mitosis. A GFP fusion protein with the ESCRT III subunit CHMP4B accumulated at the sites where nuclear integrity was lost. Moreover, depletion of ESCRT III subunits that impair the recruitment of the ESCRT III machinery led to increased nuclear GFP leakage and a prolonged cytoplasmic GFP signal after cells had passed through a constriction, indicating that ESCRT III is important for restoring nuclear membrane integrity in migrating cells.

Lastly, both groups investigated the consequences of nuclear envelope opening for DNA damage. When imaging cells expressing fluorescently labelled 53BP1, a protein recruited to double-strand breaks, both groups observed a transient increase in the number and intensity of 53BP1–GFP foci, suggesting that nuclear envelope opening induces DNA damage. Importantly, inhibition of ESCRT III-mediated nuclear envelope repair or DNA damage repair alone did not reduce cell viability, but inhibition of both pathways induced cell death after nuclear envelope rupture.

Together, these studies show that the migration of cells through confining spaces involves the rupture and ESCRT III-dependent resealing of the nuclear envelope, and that the impairment of both nuclear envelope and DNA damage repair pathways decreases cell viability. Thus, this interphasic nuclear membrane rupture may constitute a potential weakness of metastatic cells that could be exploited for the development of anti-metastatic drugs.

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ORIGINAL ARTICLES Denais, C. M. *et al.* Nuclear envelope rupture and repair during cancer cell migration. *Science* http://dx.doi.org/10.1126/science.aad7297 (2016) | Raab, M. *et al.* ESCRT III repairs nuclear envelope ruptures during cell migration to limit DNA damage and cell death. *Science* http://dx.doi.org/10.1126/science.aad7611 (2016)