

Cells set sail after lifting anchor from Myo1E

Study reveals that ERK signaling promotes cell migration by regulating motor protein's localization.

FOCAL POINT

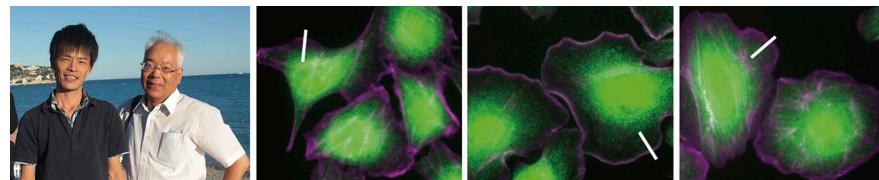


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Many different signaling molecules can induce cell migration by activating the small GTPase Ras, which in turn activates both phosphatidylinositol 3-kinase (PI3K) and extracellular signal-regulated kinase (ERK) pathways. The PI3K pathway stimulates actin polymerization and the formation of a lamellipodial protrusion at the leading edge of the cell, but how ERK signaling promotes cell motility is less well understood. Tanimura et al. now reveal that one function of the ERK pathway is to inactivate a negative regulator of the myosin Myo1E, allowing the motor protein to move to the tips of lamellipodia where it can facilitate cell movement (1).

Susumu Tanimura and Michiaki Kohno, from Nagasaki University in Japan, first demonstrated that ERK signaling promotes cell migration in 1998 (2). Since then, ERK has been shown to phosphorylate several components of the cell's motility machinery, such as myosin light chain kinase, cortactin, and focal adhesion kinase. More recently, Tanimura et al. discovered that a downstream component of the ERK pathway, p90 ribosomal S6 kinase (RSK) phosphorylates and inactivates an inhibitor of cell migration called SH3P2 (3). "We now wanted to uncover the precise molecular mechanism by which SH3P2 inhibits cell motility," Kohno says.

Tanimura et al. therefore looked for binding partners of SH3P2 using a GST-based pull down assay (1), and found that the protein binds to the class I myosin Myo1E, which has previously been implicated in cell migration (4). Using a series of deletion mutants, the researchers determined that the two proteins interacted with each other via two distinct interfaces. "The proline-rich region of SH3P2 interacts with the SH3 domain of Myo1E, and a C-terminal acidic amino acid cluster of SH3P2 binds to a positively charged region

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in the TH2 domain of Myo1E's C-terminal tail," Kohno explains.

Upon activation of the ERK pathway, RSK phosphorylates a serine residue near to this C-terminal acidic patch in SH3P2, potentially disrupting the interaction with Myo1E. Indeed, ERK activation reduced the association between SH3P2 and

Myo1E, an effect that could be prevented by adding an inhibitor of the ERK signaling pathway or by expressing a nonphosphorylatable version of SH3P2.

"In the absence of ERK activation, both Myo1E and SH3P2 localize to the cytosol," says Kohno. "But phosphorylation of SH3P2 results in the dissociation of Myo1E and its subsequent relocation to the tips of lamellipodia." This relocation

promoted lamellipodial extension. Cells lacking Myo1E still formed lamellipodia, but the protrusions were poorly developed, and the cells themselves were less motile than control cells.

Myo1E's localization to lamellipodia was mediated by the protein's TH2 domain, which can bind to newly polymerized F-actin (5). SH3P2 prevents this interaction, thereby maintaining Myo1E in the cytosol. "So SH3P2 functions as a cytoplasmic

anchor for Myo1E, suppressing its localization to lamellipodial tips and thereby negatively regulating cell motility," Kohno says. In addition, Myo1E represents a point of convergence for the signaling pathways downstream of Ras, because its movement to the tips of lamellipodia also relied on the actin rearrangements induced by PI3K.

Precisely how Myo1E promotes lamellipodial extension and cell motility after its release from SH3P2 remains unclear. The motor protein's TH1 domain can bind to plasma membrane phospholipids, thereby linking the plasma membrane to the actin cytoskeleton to generate mechanical tension (6). In addition, Myo1E can bring several different cargo proteins to the plasma membrane, including dynamin and the N-WASP-WIP actin polymerization complex (4, 7–8). "We're currently trying to identify additional effector molecules that are transported or recruited by Myo1E to induce cell migration," Tanimura says.

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